09/148234
AH#25

1. Document ID: US 20010041668 A1

L7: Entry 1 of 46

File: PGPB

Nov 15, 2001

PGPUB-DOCUMENT-NUMBER: 20010041668
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20010041668 A1

TITLE: METHODS FOR MODULATING HEMATOPOIESIS AND VASCULAR GROWTH

PUBLICATION-DATE: November 15, 2001
US-CL-CURRENT: 514/2; 435/7.2, 514/44

APPL-NO: 09/ 021660
DATE FILED: February 10, 1998
CONTINUED PROSECUTION APPLICATION: CPA

IN: BARON, MARGARET H., FARRINGTON, SARAH M., BELAUSSOFF, MARIA

AB: This application pertains to methods and compositions that modulate proliferation
and/or differentiation of undifferentiated mesodermally-derived cells so as to have an effect
on at least one of vascular growth and hematopoiesis.

L7: Entry 1 of 46

File: PGPB

Nov 15, 2001

DOCUMENT-IDENTIFIER: US 20010041668 A1
TITLE: METHODS FOR MODULATING HEMATOPOIESIS AND VASCULAR GROWTH

DRTX:
[0036] FIG. 17 shows the results of a rescue experiment using null mutant embryonic stem cells (ES)
and adding back recombinant BMP-4 to the culture. (A) and (C) shows wild type embryoid bodies that
arise from embryonic stem cells isolated from a wild type mouse. In (B) the embryonic stem cells are
homozygous BMP-4 deficient. and the embryoid bodies lack detectable blood formation. In (D), BMP-4
protein is added to the embryoid bodies of (B) and blood formation is observed.

2. Document ID: US 6331612 B1

L7: Entry 2 of 46

File: USPT

Dec 18, 2001

US-PAT-NO: 6331612
DOCUMENT-IDENTIFIER: US 6331612 B1
TITLE: Bone morphogenic protein-16 (BMP-16) compositions
DATE-ISSUED: December 18, 2001

US-CL-CURRENT: 530/350; 530/351

APPL-NO: 9/ 328775
DATE FILED: June 9, 1999

PARENT-CASE:

This application is a divisional of U.S. Ser. No. 08/715,202 filed Sep. 18, 1996, now U.S. Pat. No.
5,965,403.

2/01/02

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-16 proteins and processes for producing them are disclosed. DNA
molecules encoding the BMP-16 proteins are also disclosed. The proteins may be used in the
treatment of bone, cartilage, other connective tissue defects and disorders, including tendon,
ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of
disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac
muscle, and other tissues and wounds, and organs such as liver, lung, cardiac, pancreas and
kidney tissue. The proteins may also be useful for the induction of growth and/or
differentiation of undifferentiated embryonic and stem cells.

L7: Entry 2 of 46

File: USPT

Dec 18, 2001

DOCUMENT-IDENTIFIER: US 6331612 B1
TITLE: Bone morphogenic protein-16 (BMP-16) compositions

BSPR:
The BMP-16 DNA sequence (SEQ ID NO: 1) and amino acid sequence (SEQ ID NO: 2) are set forth in the
Sequence Listings. BMP-16 proteins may be capable of inducing the formation of cartilage, bone, or
other connective tissue, or combinations thereof. The cartilage and/or bone and/or other connective
tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be
further characterized by the ability to demonstrate effects upon the growth and/or differentiation
of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention
may also be useful for treating cell populations, such as embryonic cells or stem cell populations,
to enhance or enrich the growth and/or differentiation of the cells.

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human BMP-16
protein. The invention, therefore, includes methods for obtaining the DNA sequences encoding human
BMP-16 protein, the DNA sequences obtained by those methods, and the human protein encoded by those
DNA sequences. This method entails utilizing the human BMP-16 protein nucleotide sequence or
portions thereof to design probes to screen libraries for the corresponding gene from other species
or coding sequences or fragments thereof from using standard techniques. Thus, the present invention
may include DNA sequences from other species, which are homologous to human BMP-16 protein and can
be obtained using the human BMP-16 sequence. The present invention may also include functional
fragments of the human BMP-16 protein, and DNA sequences encoding such functional fragments, as well
as functional fragments of other related proteins. The ability of such a fragment to function is
determinable by assay of the protein in the biological assays described for the assay of the BMP-16
protein. A DNA sequence encoding the complete mature human BMP-16 protein (SEQ ID NO:1) and the
corresponding amino acid sequence (SEQ ID NO:2) are set forth herein. The BMP-16 proteins of the
present invention, such as human BMP-16, may be produced by culturing a

cell transformed with the
correlating DNA sequence, such as the human BMP-16 DNA sequence, and recovering and purifying
protein, such as BMP-16, from the culture medium. The purified expressed protein is substantially
free from other proteinaceous materials with which it is co-produced, as well as from other
contaminants. The recovered purified protein is contemplated to exhibit cartilage and/or bone and/or
connective tissue formation activity. Thus, the proteins of the invention may be further
characterized by the ability to demonstrate cartilage and/or bone and/or other connective tissue
formation activity in the rat bone formation assay described below. BMP-16 proteins may be further
characterized by the ability to demonstrate effects upon the growth and/or differentiation of
embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may
also be characterized by their ability to enhance or enrich the growth and/or differentiation of the
cells.

BSPR:
The purified proteins of the present inventions may be used to generate antibodies, either
monoclonal or polyclonal, to human BMP-16 and/or other BMP-16-related proteins, using methods that
are known in the art of antibody production. Thus, the present invention also includes antibodies to
human BMP-16 and/or other related proteins. The antibodies may be useful for purification of BMP-16
and/or other BMP-16 related proteins, or for inhibiting or preventing the effects of BMP-16 related
proteins. The BMP-16 protein and related proteins may be useful for inducing the growth and/or
differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the
present invention may also be useful for treating relatively undifferentiated cell populations, such
as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation
of the cells. The treated cell populations may be useful for implantation and for gene therapy
applications.

BSPR:
The BMP-16 proteins recovered from the culture medium are purified by isolating them from other
proteinaceous materials from which they are co-produced and from other contaminants present. BMP-16
proteins may be characterized by the ability to induce the formation of cartilage and/or bone and/or
other connective tissue and other tissue repair and differentiation, for example, in the rat bone
formation assay described below. In addition, BMP-16 proteins may be further characterized by their
effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the
proteins or compositions of the present invention may be characterized by the embryonic stem cell
assay described below.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

DEPR:
In order to assay the effects of the BMP-16 proteins of the present invention, it is possible to
assay the growth and differentiation effects in vitro on a number of available embryonic stem cell
lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection
in Rockville, Md.

3. Document ID: US 6322786 B1

L7: Entry 3 of 46

File: USPT

Nov 27, 2001

US-PAT-NO: 6322786
DOCUMENT-IDENTIFIER: US 6322786 B1
TITLE: Method of producing bone-inducing agent
DATE-ISSUED: November 27, 2001

US-CL-CURRENT: 424/115; 424/573, 435/366, 514/2, 514/21

APPL-NO: 8/ 799343
DATE FILED: February 13, 1997

PARENT-CASE:
This application claims the benefit of U.S. provisional application No. 60/011,703, filed on Feb.
15, 1996.

IN: Anderson; H. C.

AB: The present invention provides methods to isolate and purify components required for
bone-induction using extracts of Saos-2 cells or proteins released by Saos-2 cells into
conditioned tissue culture medium. In addition, the present invention provides a method of
augmenting bone growth locally comprising implanting the near osteoprogenitor cells the bone
inducing agent isolated in the methods of the present invention, together with a mechanically
suitable biodegradable carrier.

L7: Entry 3 of 46

File: USPT

Nov 27, 2001

DOCUMENT-IDENTIFIER: US 6322786 B1
TITLE: Method of producing bone-inducing agent

DEPR:
Certain BMPs have been shown to stimulate the expression of osseous phenotypic traits by cultured
marrow stromal osteoprogenitor cells (31). Also, preosteoblastic cell lines have been induced by
BMPs to express alkaline phosphatase (ALP) and other molecular markers

of bone cell differentiation.
These include primary rat osteoblast cells by BMP-2 or BMP-3 (9,39,43,48), and W-20-17 or C3H,
10T1/2 pluripotent mouse mesenchymal stem cells (23,60). Exposure to purified extracts of Saos-2
cells or fractions derived from Saos-2 cell conditioned culture media is capable of stimulating
osseous differentiation by one or more of these cells. Establishing a system of in vitro bone
induction using the Saos-2 cell bone-inducing agent provides a more quantifiable bioassay method for
testing the osteoinductivity of various fractions and isolates of bone inducing agent. Furthermore,
such an in vitro assay is ideal to study the mechanism of osteoinduction under defined conditions at
the cellular level, e.g., bone inducing agent receptors, method of signal transduction, etc.

4. Document ID: US 6294320 B1

L7: Entry 4 of 46
File: USPT
Sep 25, 2001

US-PAT-NO: 6294320
DOCUMENT-IDENTIFIER: US 6294320 B1
TITLE: Cell matrix plaques of initial bone formation
DATE-ISSUED: September 25, 2001

US-CL-CURRENT: 435/4; 435/343, 435/343.1, 530/388.7

APPL-NO: 9/ 454330
DATE FILED: December 3, 1999

PARENT-CASE:
The contents of Applicant's provisional application Ser. No. 60/110,878 filed Dec. 4, 1998 are
hereby incorporated by reference.

IN: Hruska; Keith, Wozniak; Magdalena

AB: An isolated and essentially purified cell matrix plaque of initial bone formation
comprising of .alpha..sub.v.beta..sub.3 integrin and rapid assays using such cell matrix
plaques to measure potentials of factors, regimens or tissues for stimulation and/or inhibition
of bone formation.

L7: Entry 4 of 46
File: USPT
Sep 25, 2001

DOCUMENT-IDENTIFIER: US 6294320 B1
TITLE: Cell matrix plaques of initial bone formation

DEPR:
Utilizing this discovery, a method of measuring new bone formation using a rapid in vitro assay has
been developed. The method involves extracting bone marrow stromal cells from bone marrow cavities
and growing them to semi-confluence; exposing the cells to a candidate medium or regimen for
osteogenesis or inhibition of osteogenesis; determining the mineralization/development of bone
plaque; and, optionally, comparing the mineralization/development of bone plaque generated using the
candidate medium or regimen with the mineralization/development of bone plaque using a preselected
control such as bone morphogenetic factor-7 (BMP-7), also known as osteogenic factor-1 (OP-1).

DEPR:
Bone marrow stromal cells grown to semi-confluence and then exposed to osteogenic medium containing
10 mM of .beta.-glycerophosphate, 50 .mu.g/ml ascorbic acid and 40 ng/ml of osteogenic protein
OP-1(32) also referred to as bone morphogenetic protein-7 (BMP-7), for 48 hours were defined as
preosteoblasts. These prcosteoblast cultures are characterized by alkaline phosphatase activity of
80,000 nmole pNPP/min./.mu.g protein, osteopontin expression, absence of osteocalcin expression, and
mineralization after 14 days in osteogenic media. For the purposes of this paper, bone marrow
stromal cells exposed to OP-1-containing osteogenic medium for 14 days were defined as "mineralizing
preosteoblasts" or osteoblasts. The osteoblast cultures are characterized by alkaline phosphatase
activity of 60,000 nmole pNPP/min./.mu.g protein, osteopontin expression, osteocalcin expression and
mineralization of the extracellular matrix.

5. Document ID: US 6291206 B1

L7: Entry 5 of 46
File: USPT
Sep 18, 2001

US-PAT-NO: 6291206
DOCUMENT-IDENTIFIER: US 6291206 B1
TITLE: BMP receptor proteins
DATE-ISSUED: September 18, 2001

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 536/23.1, 536/23.5, 536/23.51

APPL-NO: 8/ 123934
DATE FILED: September 17, 1993

IN: Wozney; John M., Celeste; Anthony J., Thies; R. Scott, Yamaji; Noboru

AB: Novel serine/threonine receptor proteins and BMP receptor proteins are disclosed, as
well as DNA molecules encoding said proteins and methods of using the receptor proteins.
Further disclosed are truncated BMP receptor proteins and molecules which act as ligands to
said BMP receptor proteins.

L7: Entry 5 of 46
File: USPT
Sep 18, 2001

DOCUMENT-IDENTIFIER: US 6291206 B1
TITLE: BMP receptor proteins

DEPR:
Use of the W-20-17 bone marrow stromal cells as an indicator cell line is based upon the conversion
of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology,

130:1318 (1992)].
Specifically, W-20-17 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of
W-20-17 cells with certain BMP proteins results in (1) increased alkaline phosphatase production,
(2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While
(1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20-17 stromal cells to osteoblastlike cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20-17 cells
correlate with the in vivo bone forming activity known for BMPs.

6. Document ID: US 6287816 B1

L7: Entry 6 of 46

File: USPT

Sep 11, 2001

US-PAT-NO: 6287816
DOCUMENT-IDENTIFIER: US 6287816 B1
TITLE: BMP-9 compositions
DATE-ISSUED: September 11, 2001

US-CL-CURRENT: 435/69.4; 424/423, 424/426, 424/484, 435/252.3, 435/320.1, 435/325, 514/12, 530/399,
530/840, 536/23.51, 536/24.31, 930/120

APPL-NO: 8/ 254353
DATE FILED: June 6, 1994

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No.
08/050,132 filed Apr. 22, 1993 now U.S. Pat. No. 5,661,007 which is a continuation-in-part of U.S.
Ser. No. 07/720,590 filed Jun. 25, 1991, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
WO	PCT/US92/05374	June 25, 1992

IN: Rosen; Vicki A., Wozney; John M., Celeste; Anthony J., Thies; R. Scott, Song;
Jeffrey R.

AB: Purified bone morphogenetic protein-9 (BMP-9) proteins and processes for producing
them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and
in wound healing and related tissue repair.

L7: Entry 6 of 46

File: USPT

Sep 11, 2001

DOCUMENT-IDENTIFIER: US 6287816 B1

TITLE: BMP-9 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone
Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and
Mineral Research 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic
Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press
(1992)). Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice
by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2
treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of
PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2)
represent characteristics associated with the osteoblast phenotype, the ability to synthesize
osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we
have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with
BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the
in vivo bone forming activity known for BMPS.

7. Document ID: US 6261586 B1

L7: Entry 7 of 46

File: USPT

Jul 17, 2001

US-PAT-NO: 6261586
DOCUMENT-IDENTIFIER: US 6261586 B1
TITLE: Bone graft composites and spacers
DATE-ISSUED: July 17, 2001

US-CL-CURRENT: 424/423; 424/422, 424/426, 424/548, 424/549, 514/2, 523/115, 530/840, 606/61,
623/17.12

APPL-NO: 9/ 386560
DATE FILED: August 31, 1999

PARENT-CASE:
This application is a continuation of applicants' U.S. patent application Ser. No. 08/873,276, filed
Jun. 11, 1997, now U.S. Pat. No. 5,972,368.

IN: McKay; William F.

AB: A bone graft substitute including a composition of natural selectively deactivated
bone material which has been processed to remove associated non-collagenous bone proteins, said
bone material containing native collagen materials and naturally associated bone minerals and
substantially free from native non-collagenous protein, and a therapeutically effective amount
to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier in
synergistic combination with said bone material. Spacers composed of the bone graft substitute
composition methods for using the spacers are also provided.

L7: Entry 7 of 46

File: USPT

Jul 17, 2001

DOCUMENT-IDENTIFIER: US 6261586 B1
TITLE: Bone graft composites and spacers

DEPR:
This invention provides the further advantage of exploiting the discovery that bone mineral is an
excellent carrier for osteogenic factors such as bone morphogenic proteins. Hydroxyapatite which is
very similar in chemical composition to the mineral in cortical bone is an osteogenic factor-binding
agent which controls the rate of delivery of certain proteins to the fusion site. Calcium phosphate
compositions such as hydroxyapatite are thought to bind bone morphogenic proteins and prevent BMP
from prematurely dissipating from the spacer before fusion can occur. It is further believed that
retention of the BMP by the agent permits the protein to initiate the transformation of mesenchymal
stem cells into bone producing cells or osteoblasts within the device at a rate that is conducive to
complete and rapid bone formation and ultimately, fusion across the disc space. The spacers of this
invention have the advantage of including a load bearing member composed of selectively deactivated
bone which naturally binds and provides controlled delivery of osteogenic factors such as bone
morphogenic proteins.

8. Document ID: US 6251671 B1

L7: Entry 8 of 46

File: USPT

Jun 26, 2001

US-PAT-NO: 6251671
DOCUMENT-IDENTIFIER: US 6251671 B1
TITLE: Compositions and methods of making embryonic stem cells
DATE-ISSUED: June 26, 2001

US-CL-CURRENT: 435/384; 435/385, 435/386, 435/387

APPL-NO: 8/ 808346
DATE FILED: February 28, 1997

PARENT-CASE:
This Application claims the benefit of U.S. Provisional applications 60/012386 Filed Feb. 28, 1996
and 60/012,384 filed Feb. 28, 1996.

IN: Hogan; Brigid L. M., Zhao; Guang-Quan

AB: The invention relates to cell proliferation, cell differentiation, male infertility,
male fertility and to compositions and methods involved therein. Also methods of culturing
spermatogonial stem cells with bone morphogenetic protein 8 are disclosed.

L7: Entry 8 of 46

File: USPT

Jun 26, 2001

DOCUMENT-IDENTIFIER: US 6251671 B1
TITLE: Compositions and methods of making embryonic stem cells

BSPR:
Mutations in other Bmp genes have been generated by homologous recombination in embryonic stem
cells. For example, Bmp7 homozygous null mutant mice die shortly after birth with major defects in
eye, kidney and limb development (Dudley et al., 1995, Genes Dev. 9:2795-2807; Luo et al., 1995,
Genes Dev. 9:2808-2820). Most Bmp4 homozygous mutant embryos die around the time of gastrulation and
many exhibit a deficiency in extraembryonic and posterior/ventral mesoderm (Winnier et al., 1995,
Genes Dev. 9:2105-2116), a finding consistent with the effect of BMP4 on mesoderm patterning in
Xenopus embryos (Jones et al., 1992, Development 115:639-647; Graff et al., 1994, Cell 79:169-179;
Harland, 1994, Proc. Natl. Acad. Sci. USA 91:10243-10246). Mutations have also been described in
other members of the BMP superfamily, including mouse nodal, and Gdf5 (brachypodism) (Zhou et al.,
1993, Nature 361:543-547; Conlon et al., 1994, Development 120:1919-1928; Storm et al., 1994, Nature
368:639-643).

BSPR:
Also included in the invention is a method of differentiating mammalian spermatogonial stem cells,
comprising culturing spermatogonial stem cells in the presence of BMP, or a biologically active
fragment or an agonist thereof, to effect differentiation of the cells.

9. Document ID: US 6190880 B1

L7: Entry 9 of 46

File: USPT

Feb 20, 2001

US-PAT-NO: 6190880
DOCUMENT-IDENTIFIER: US 6190880 B1
TITLE: Recombinant bone morphogenetic protein heterodimers, compositions and methods of use
DATE-ISSUED: February 20, 2001

US-CL-CURRENT: 435/69.1; 435/252.3, 435/252.33, 435/255.1, 435/320.1, 435/325, 435/70.2, 530/350,
530/399, 536/23.5

APPL-NO: 8/ 469411
DATE FILED: June 6, 1995

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation of application Ser. No.
07/989,847, filed Nov. 27, 1992, now U.S. Pat. No. 5,866,364 which is a continuation-in-part of U.S.
Ser. No. 07/864,692 filed Apr. 7, 1992, now abandoned, which is a continuation-in-part of U.S. Ser.
No. 07/787,496 filed Nov. 4, 1991, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
WO	PCT/US92/09430	November 2, 1992

IN: Israel; David, Wolfman; Neil M.

AB: The present invention relates to a methods for producing recombinant heterodimeric
BMP proteins useful in the field of treating bone defects, healing bone injury and in wound
healing in general. The invention also relates to the recombinant heterodimers and compositions
containing them.

L7: Entry 9 of 46

File: USPT

Feb 20, 2001

DOCUMENT-IDENTIFIER: US 6190880 B1
TITLE: Recombinant bone morphogenetic protein heterodimers, compositions and methods of use

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al, "Bone
Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and
Mineral Research, 5(2) :305 (1990); and R. S. Thies et al, "Recombinant Human Bone Morphogenetic
Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press
(1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice
by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2
treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of
PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2)
represent characteristics associated with the osteoblast phenotype, the ability to synthesize
osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we
have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with
BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the
in vivo bone forming activity known for BMPS.

10. Document ID: US 6179872 B1

L7: Entry 10 of 46

File: USPT

Jan 30, 2001

US-PAT-NO: 6179872
DOCUMENT-IDENTIFIER: US 6179872 B1
TITLE: Biopolymer matt for use in tissue repair and reconstruction
DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 623/11.11; 428/304.4, 442/123, 530/354, 530/356

APPL-NO: 9/ 042549
DATE FILED: March 17, 1998

IN: Bell; Eugene, Sioussat; Tracy M., Begley; Michael J.

AB: Biopolymer matt, biopolymer matt composites, biopolymer matt compositions, and
methods of preparing the matt and composite matts are described. Also described are
biocompatible constructs which include extracellular matrix macromolecules and methods of
preparing these constructs. The matt, matt compositions and biocompatible constructs of the
invention can be used in tissue repair and reconstruction.

L7: Entry 10 of 46

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6179872 B1
TITLE: Biopolymer matt for use in tissue repair and reconstruction

DEPR:
The term "growth factors" is art recognized and is intended to include, but is not limited to, one
or more of platelet derived growth factors (PDGF), e.g., PDGF AA, PDGF BB; insulin-like growth
factors (IGF), e.g., IGF-I, IGF-II; fibroblast growth factors (FGF), e.g., acidic FGF, basic FGF,
.beta.-endothelial cell growth factor, FGF 4, FGF 5, FGF 6, FGF 7, FGF 8, and FGF 9; transforming
growth factors (TGF), e.g., TGF-P1, TGF-.beta.1.2, TGF-.beta.2, TGF-.beta.3, TGF-.beta.5; bone
morphogenic proteins (BMP), e.g., BMP 1, BMP 2, BMP 3, BMP 4; vascular endothelial growth factors
(VEGF), e.g., VEGF, placenta growth factor; epidermal growth factors (EGF), e.g., EGF, amphiregulin,
betacellulin, heparin binding EGF; interleukins, e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7,
IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14; colony stimulating factors (CSF), e.g., CSF-G,
CSF-GM, CSF-M; nerve growth factor (NGF); stem cell factor; hepatocyte growth factor, and ciliary
neurotrophic factor. The term encompasses presently unknown growth factors that may be discovered in
the future, since their characterization as a growth factor will be readily determinable by persons
skilled in the art.

DEPR:
Growth factors necessary for cell growth are attached to structural elements of the extracellular
matrix. The structural elements include proteins, e.g., collagen and elastin, glycoproteins,
proteoglycans and glycosaminoglycans. The growth factors, originally produced and secreted by cells,
bind to the extracellular matrix and regulate cell behavior in a number of ways. These factors
include, but are not limited to, one or more of platelet derived growth factors (PDGF), e.g., PDGF
AA, PDGF BB; insulin-like growth factors (IGF), e.g., IGF-I, IGF-II; fibroblast growth factors
(FGF), e.g., acidic FGF, basic FGF, .beta.-endothelial cell growth factor, FGF 4, FGF 5, FGF 6, FGF
7, FGF 8, and FGF 9; transforming growth factors (TGF), e.g., TGF-.beta.1, TGF-.beta.1.2,
TGF-.beta.2, TGF-.beta.3, TGF-.beta.5; bone morphogenic proteins (BMP), e.g., BMP 1, BMP 2, BMP 3,
BMP 4; vascular endothelial growth factors (VEGF), e.g., VEGF, placenta growth factor; epidermal
growth factors (EGF), e.g., EGF, amphiregulin, betacellulin, heparin binding EGF; interleukins,
e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14;
colony stimulating factors (CSF), e.g., CSF-G, CSF-GM, CSF-M; nerve growth factor (NGF); stem cell
factor; hepatocyte growth factor, and ciliary neurotrophic factor. Adams et al., "Regulation of
Development and Differentiation by the Extracellular Matrix" Development Vol. 117, p. 1183-1198
(1993) (hereinafter "Adams et al.") and Kreis et al. editors of the book

entitled "Guidebook to the
Extracellular Matrix and Adhesion Proteins," Oxford University Press (1993) (hereinafter "Kreis et
al.") describe extracellular matrix components that regulate differentiation and development.
Further, Adams et al. disclose examples of association of growth factors with extracellular matrix
proteins and that the extracellular matrix is an important part of the micro-environment and, in
collaboration with growth factors, plays a central role in regulating differentiation and
development. The teachings of Adams et al. and Kreis et al. are incorporated herein by reference.

11. Document ID: US 6165748 A

L7: Entry 11 of 46

File: USPT

Dec 26, 2000

US-PAT-NO: 6165748
DOCUMENT-IDENTIFIER: US 6165748 A
TITLE: Frazzled nucleotide sequences and expression products
DATE-ISSUED: December 26, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/254.11, 435/320.1, 435/325, 530/300, 530/350, 536/23.1,
536/23.5

APPL-NO: 8/ 893654
DATE FILED: July 11, 1997

IN: Racie; Lisa, Lavallie; Edward, Paulsen; Janet, Sive; Hazel, Sun; Benjamin

AB: Purified Frazzled proteins, including WG67-16, WG67-19 and WA628, and processes for
producing them are disclosed. DNA molecules encoding the Frazzled proteins, including WG67-16,
WG67-19 and WA628, are also disclosed. The proteins may be used in modulating the binding of
Wnt genes to their receptor. They are useful in the modulation of cellular formation, growth,
differentiation, proliferation and/or maintenance of a variety of adult and embryonic tissues
and organs.

L7: Entry 11 of 46

File: USPT

Dec 26, 2000

DOCUMENT-IDENTIFIER: US 6165748 A
TITLE: Frazzled nucleotide sequences and expression products

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with an osteogenic protein, such as a BMP
protein (Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al,
Endocrinology, 130:1318 (1992)). Specifically, W-20 cells are a clonal bone marrow stromal cell line
derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,
Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline
phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin
synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast
phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature
osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to
osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities
displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

12. Document ID: US 6083690 A

L7: Entry 12 of 46

File: USPT

Jul 4, 2000

US-PAT-NO: 6083690
DOCUMENT-IDENTIFIER: US 6083690 A
TITLE: Methods and compositions for identifying osteogenic agents
DATE-ISSUED: July 4, 2000

US-CL-CURRENT: 435/6; 435/29, 435/320.1, 435/325, 435/375, 435/4, 435/455, 536/23.1, 536/24.1

APPL-NO: 8/ 458434
DATE FILED: June 2, 1995

IN: Harris; Stephen E., Mundy; Gregory R., Ghosh-Choudhury; Nandini, Feng; Jian Q.

AB: Methods and compositions for identifying osteogenic agents are disclosed, wherein a
bone morphogenetic protein promoter is utilized in an assay system to modulate the production
of an assayable product of a reporter gene.

L7: Entry 12 of 46

File: USPT

Jul 4, 2000

DOCUMENT-IDENTIFIER: US 6083690 A
TITLE: Methods and compositions for identifying osteogenic agents

DEPR:
Several BMP-4 cDNAs were sequenced from prostate cancer cell line PC-3 and from primary FRC cells.
Four independent FRC cell BMP-4 cDNAs all contained exon 1A. However, the human prostate carcinoma
cell line (PC-3) cDNA contained an apparently unique exon 1B sequence spliced to exon 2 (Chen et al,
1993). A double-stranded oligonucleotide probe (70 bp) to exon 1B was synthesized based on the human
PC-3 exon 1B sequence. This exon 1B probe was then used to identify the exon 1B region in the mouse
genomic BMP-4 clone. The candidate exon 1B is 1696 bp downstream from the 3' end of exon 1A.

DEPR:
To analyze the activity of the BMP-2 promoter in cell types not expressing BMP-2 mRNA, BMP-2
promoter constructs were transfected into CV-1 cells (monkey kidney cells). The BMP-2 promoter
activity was found to be very low for all constructs. This suggests that this region of the BMP-2

promoter is functional only in cells such as primary fetal rat calvarial osteoblasts, HeLa and ROS
17/2.8 that express endogenous BMP-2 mRNA (Anderson & Coulter 1968). CV-1 cells do not express BMP-2
mRNA. The BMP-2 promoter is likely active in other cell types that express BMP-2, such as prostate
cells and chondrocytes, although regulation of transcription may be different in these cells.

Rickard, D.J. et al., "Induction of Rapid Osteoblast Differentiation in Rat Bone Marrow Stromal Cell
Cultures by Dexamethasone and BMP-2," Developmental Biology (1994) 161:218-228.

13. Document ID: US 6080779 A

L7: Entry 13 of 46

File: USPT

Jun 27, 2000

US-PAT-NO: 6080779
DOCUMENT-IDENTIFIER: US 6080779 A
TITLE: Compositions and methods for stimulating bone growth
DATE-ISSUED: June 27, 2000

US-CL-CURRENT: 514/451; 514/141, 514/185, 514/700

APPL-NO: 9/ 096957
DATE FILED: June 12, 1998

PARENT-CASE:
This application claims priority under 35 USC 119 from provisional application Ser. No. 60/032,893
filed Dec. 13, 1996. It is also a continuation-in-part of U.S. Ser. No. 08/989,862 filed Dec. 12,
1997 claiming benefit under 35 USC 120. The entire contents of these documents are incorporated
herein by reference.

IN: Gasper; Shirley R., West; Robert R., Martinez; Theresa, Robbins; Kirk G., McKernan;
Patricia A., Baindur; Nand, Labroo; Virender M., Mundy; Gregory R.

AB: Compounds of the formula ##STR1## wherein X in each of formulas (1) and (2)
represents a substituted or unsubstituted alkylene, alkenylene, or alkynylene linker of 2-6 C;,
Y represents one or more carbocyclic or heterocyclic rings; when two or more rings are present
in Y, they may optionally be fused; and, R' represents a cation, H or a substituted or
unsubstituted alkyl group of 1-6 C; and, the dotted lines represent optional .pi.-bonds,,
promote bone formation and are thus useful in treating osteoporosis, bone fracture or
deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic
bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and
post-dental implantation. These compounds can be used in combination with other bone
growth-promoting compounds and/or estrogens and/or bisphosphonates for this purpose.

L7: Entry 13 of 46

File: USPT

Jun 27, 2000

DOCUMENT-IDENTIFIER: US 6080779 A
TITLE: Compositions and methods for stimulating bone growth

ORPL:

14. Document ID: US 6077987 A

L7: Entry 14 of 46

File: USPT

Jun 20, 2000

US-PAT-NO: 6077987
DOCUMENT-IDENTIFIER: US 6077987 A
TITLE: Genetic engineering of cells to enhance healing and tissue regeneration
DATE-ISSUED: June 20, 2000

US-CL-CURRENT: 623/23.72; 424/422, 424/423, 424/93.21, 623/23.57, 623/23.6

APPL-NO: 8/ 923718
DATE FILED: September 4, 1997

IN: Breitbart; Arnold S., Grande; Daniel S., Mason; James M.

AB: A method for enhancing and/or increasing the efficiency of repair of tissues,
primarily bone or cartilage, using genetically engineered cells has been developed. In the
preferred embodiment, mesenchymal stem cells are isolated from periosteum tissue, and
transfected with the gene encoding a growth factor for the particular cell type to be repaired.
For example, for repair of bone, a gene (or genes) encoding bone morphogenic protein is
transfected into periosteal cells. The transfected periosteal cells then express the bone
morphogenic protein in culture to promote bone repair as a function of the expressed bone
morphogenic protein. Cells can be transfected using any appropriate means, including viral
vectors, as shown by the example, chemical transfectants, or physico-mechanical methods such as
electroporation and direct diffusion of DNA. Genes can encode any useful protein, for example,
a specific growth factor, morphogenesis factor, a structural protein, or a cytokine which
enhances the temporal sequence of wound repair, alters the rate of proliferation, increases the
metabolic synthesis of extracellular matrix proteins, or directs phenotypic expression in
endogenous cell populations. Representative genes encoding proteins include bone growth factor
genes, cartilage growth factor genes, nerve growth factor genes, and general growth factors
important in wound healing, such as platelet-derived growth factor (PDGF), vascular endothelial
growth factor (VEGF), insulin-like growth factor (IGF-1), epidermal growth factor (EGF), basic
fibroblast growth factor (FGF), endothelial derived growth supplement.

L7: Entry 14 of 46

File: USPT

Jun 20, 2000

DOCUMENT-IDENTIFIER: US 6077987 A
TITLE: Genetic engineering of cells to enhance healing and tissue regeneration

BSPR:
Preferred examples for bone repair and/or treatment of osteoporosis uses periosteal or other
mesenchymal stem cells or osteocytes/osteoblasts transfected with bone growth factor genes such as
bone morphogenetic protein (BMP) family genes, including BMP 2-15; for cartilage repair uses
periosteal cells or chondrocytes transfected with cartilage growth factor genes such as transforming
growth factor-.beta. (TGF-.beta.) and cartilage growth factor (CGF); for wound healing uses dermal
or epidermal cells transfected with growth factor genes such as platelet derived growth factor
(PDGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), keratinocyte
growth factor (KGF), fibroblast growth factor (FGF), endothelial derived growth supplement (EDGS),
or insulin-like growth factor (IGF); for nerve repair (central and/or peripheral) uses neural cells
and neural support cells transfected with nerve growth factor (NGF) gene.

15. Document ID: US 6034229 A

L7: Entry 15 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034229
DOCUMENT-IDENTIFIER: US 6034229 A
TITLE: BMP-15 compositions
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 536/23.5

APPL-NO: 8/ 982987
DATE FILED: December 2, 1997

PARENT-CASE:
This application is a continuation of U.S. Ser. No. 08/798,665, filed Feb. 11, 1997 and now, which
application is a divisional of U.S. Ser. No. 08/446,924, filed May 18, 1995 and now issued as U.S.
Pat. No. 5,635,372.

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA
molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in
the treatment of bone and cartilage and/or other connective tissue defects and in wound healing
and related tissue repair.

L7: Entry 15 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034229 A
TITLE: BMP-15 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

16. Document ID: US 6034062 A

L7: Entry 16 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034062
DOCUMENT-IDENTIFIER: US 6034062 A
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 514/12; 530/350, 530/399, 930/120

APPL-NO: 8/ 815652
DATE FILED: March 13, 1997

IN: Thies; R. Scott, Song; Jeffrey J.

AB: Purified Bone Morphogenetic Protein (BMP)-9 proteins and processes for producing
them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and
in wound healing and related tissue repair, and in hepatic growth and function.

L7: Entry 16 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034062 A
TITLE: Bone morphogenetic protein (BMP)-9 compositions and their uses

DEPR:
Human BMP-9 may be produced by culturing a cell transformed with a DNA sequence comprising
nucleotide #124 to #453 as shown in SEQ ID NO:8 and recovering and purifying from the culture medium
a protein characterized by the amino acid sequence of SEQ ID NO:9 from amino acid #1 to amino acid
#110 substantially free from other proteinaceous materials with which it is co-produced. For
production in mammalian cells, the DNA sequence further comprises a DNA sequence encoding a suitable
propeptide 5' to and lined in frame to the nucleotide sequence encoding the mature BMP-9-related
polypeptide. The propeptide may be the native BMP-9-related propeptide,

or may be a propeptide from
another protein of the TGF-.beta. superfamily. BMP-9 proteins may be characterized by the ability to
induce the formation of cartilage. BMP-9 proteins may be further characterized by the ability to
induce the formation of bone. BMP-9 proteins may be further characterized by the ability to
demonstrate cartilage and/or bone formation activity in the rat bone formation assay described
below. BMP-9 proteins may be further characterized by the ability to demonstrate effects upon the
growth and/or differentiation of embryonic cells and/or stem cells. The proteins or compositions of
the present invention may also be useful for treating cell populations, such as embryonic cells or
stem cell populations, to enhance or enrich the growth and/or differentiation of the cells.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone
Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and
Mineral Research 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic
Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology,
130(3):1318-1324 (1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line
derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,
Boston, Mass. BMP-2 treatment of W-20 cells results in (1) increased alkaline phosphatase
production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the
cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the
ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts.
Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only
upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20
cells correlate with the in vivo bone forming activity known for BMPs.

DEPR:
To determine if this proliferative effect of BMP-9 was unique to the HepG2 liver tumor cell line,
primary rat hepatocytes were tested for effects of BMP-9 on .sup.3 H-thymidine incorporated as shown
in FIG. 4. BMP-9 stimulated .sup.3 h-thymidine incorporation in primary hepatocytes, although not as
markedly as EGF. This stimulatory effect is cell density-dependent in primary rat hepatocytes. While
subconfluent cells exhibited a stimulation in response to BMP-9, confluent primary hepatocytes did
not. As indicated in FIG. 4, in contrast to rhBMP-9, TGF-.beta.1 was inhibitory, not stimulatory on
primary rat hepatocytes.

DEPR:
In order to assay the effects of the BMP-9 proteins of the present invention, it is possible to
assay the growth and differentiation effects in vitro on a number of available embryonic stem cell
lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection
in Rockville, Md.

17. Document ID: US 6034061 A

L7: Entry 17 of 46

File: USPT

Mar 7, 2000

US-PAT-NO: 6034061
DOCUMENT-IDENTIFIER: US 6034061 A
TITLE: BMP-9 compositions
DATE-ISSUED: March 7, 2000

US-CL-CURRENT: 514/12; 424/423, 424/426, 435/69.4, 514/2, 530/399, 530/840, 536/23.51, 536/24.31,
930/120

APPL-NO: 8/ 750222
DATE FILED: December 4, 1996

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a 371 of PCT/US95/07084, filed Jun. 5,
1995; which is a continuation of U.S. Ser. No. 08/254,353, filed Jun. 6, 1994; which is a
continuation of U.S. Ser. No. 08/050,132, filed Apr. 22, 1993 now abandoned (U.S. Pat. No.
5,661,007); which is a continuation-in-part of PCT/US92/05374 filed Jun. 25, 1992; which is a
continuation-in-part of Ser. No. 07/720,590, filed Jun. 25, 1991, now abandoned.

IN: Rosen; Vicki A., Wozney; John M., Celeste; Anthony J., Thies; Scott R., Song;
Jeffrey R.

AB: Purified Bone Morphogenetic Protein (BMP)-9 proteins and processes for producing
them are disclosed. The proteins may be used in the treatment of bone and cartilage defects and
in wound healing and related tissue repair, and in hepatic growth and function.

L7: Entry 17 of 46

File: USPT

Mar 7, 2000

DOCUMENT-IDENTIFIER: US 6034061 A
TITLE: BMP-9 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al., "Bone
Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and
Mineral Research 5(2):305 (1990); and R. S. Thies et al., "Recombinant Human Bone Morphogenetic
Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press
(1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice
by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, MA. BMP-2 treatment
of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of PTH
stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2)
represent characteristics associated with the osteoblast phenotype, the ability to synthesize
osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we
have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with
BMPs. In this manner, the in vitro activities displayed by BMP treated

W-20 cells correlate with the
in vivo bone forming activity known for BMPs.

DEPR:
To determine if this proliferative effect of BMP-9 was unique to the HepG2 liver tumor cell line,
primary rat hepatocytes were tested for effects of BMP-9 on .sup.3 H-thymidine incorporated as shown
in FIG. 7. BMP-9 stimulated .sup.3 h-thymidine incorporation in primary hepatocytes, although not as
markedly as EGF. This stimulatory effect is cell density-dependent in primary rat hepatocytes. While
subconfluent cells exhibited a stimulation in response to BMP-9, confluent primary hepatocytes did
not. As indicatedin FIG. 7, in contrast to rhBMP-9, TGF-.beta.1 was inhibitory, not stimulatory on
primary rat hepatocytes.

18. Document ID: US 6027917 A

L7: Entry 18 of 46

File: USPT

Feb 22, 2000

US-PAT-NO: 6027917
DOCUMENT-IDENTIFIER: US 6027917 A
TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions
DATE-ISSUED: February 22, 2000

US-CL-CURRENT: 435/69.1; 435/252.3, 435/325, 536/23.5, 536/23.51

APPL-NO: 8/ 987904
DATE FILED: December 10, 1997

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-17 and BMP-18 proteins and processes for producing them are disclosed.
DNA molecules encoding the BMP-17 and BMP-18 proteins are also disclosed. The proteins may be
used in the treatment of bone, cartilage, other connective tissue defects and disorders,
including tendon, ligament and meniscus, in wound healing and related tissue repair, as well as
for treatment of disorders and defects to tissues which include epidermis, nerve, muscle,
including cardiac muscle, and other tissues and wounds, and organs such as liver, lung,
epithelium, brain, spleen, cardiac, pancreas and kidney tissue. The proteins may also be useful
for the induction of growth and/or differentiation of undifferentiated embryonic and stem
cells.

L7: Entry 18 of 46

File: USPT

Feb 22, 2000

DOCUMENT-IDENTIFIER: US 6027917 A
TITLE: Bone morphogenetic protein (BMP)-17 and BMP-18 compositions

BSPR:
The BMP-17 (SEQ ID NO: 1) and BMP-18 (SEQ ID NO: 3) DNA sequences and amino acid sequences (SEQ ID
NO: 2 and 4, respectively) are set forth in the Sequence Listings. BMP-17 and BMP-18 proteins may be
capable of inducing the formation of cartilage, bone, or other connective tissue, or combinations
thereof. The cartilage and/or bone and/or other connective tissue formation activity in the rat bone
formation assay described below. BMP-17 and BMP-18 proteins may be further characterized by the
ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem
cells. Thus, the proteins or compositions of the present invention may also be useful for treating
cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth
and/or differentiation of the cells. Alternatively, the proteins or compositions of the present
invention may also be useful for maintenance of a cell population, including differentiated cell
populations, for example, neuronal cells, epithelial cells, dendritic cells, chondrocytes,
osteocytes, muscle cells or cells of other differentiated phenotypes.

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human BMP-17
and BMP-18 protein. The invention, therefore, includes methods for obtaining the DNA sequences
encoding human BMP-17 and BMP-18 proteins, the DNA sequences obtained by those methods, and the
human proteins encoded by those DNA sequences. This method entails utilizing the human BMP-17 and
BMP-18 nucleotide sequences or portions thereof to design probes to screen libraries for the
corresponding gene from other species or coding sequences or fragments thereof from using standard
techniques. Thus, the present invention may include DNA sequences from other species, which are
homologous to human BMP-17 and BMP-18 proteins and can be obtained using the human BMP-17 and/or
BMP-18 sequences. The present invention may also include functional fragments of the human BMP-17
and BMP-18 proteins, and DNA sequences encoding such functional fragments, as well as functional
fragments of other related proteins. The ability of such a fragment to function is determinable by
assay of the protein in the biological assays described for the assay of the BMP-17 and BMP-18
proteins. DNA sequences encoding the complete mature human BMP-17 (SEQ ID NO: 1 and BMP-18 protein
(SEQ ID NO:3) and the corresponding amino acid sequences (SEQ ID NO:2 and 4, respectively) are set
forth herein. The BMP-17 and BMP-18 proteins of the present invention, such as human BMP-17 and
BMP-18, may be produced by culturing a cell transformed with the correlating DNA sequence, such as
the human BMP-17 and BMP-18 DNA sequence, and recovering and purifying protein, such as BMP-17 or
BMP-18, from the culture medium. The purified expressed protein is substantially free from other
proteinaceous materials with which it is co-produced, as well as from other contaminants. The
recovered purified protein is contemplated to exhibit cartilage and/or bone and/or connective tissue
formation activity. Thus, the proteins of the invention may be further characterized by the ability
to demonstrate cartilage and/or bone and/or other connective tissue formation activity in the rat
bone formation assay described below. BMP-17 and BMP-18 proteins may be further characterized by the
ability to demonstrate effects upon the growth and/or differentiation of embryonic cells and/or stem
cells. Thus, the proteins or compositions of the present invention may also be characterized by
their ability to enhance or enrich the growth and/or differentiation of the cells.

BSPR:
The purified proteins of the present inventions may be used to generate antibodies, either
monoclonal or polyclonal, to human BMP-17 and/or BMP-18 and/or other BMP-17 and/or BMP-18-related

proteins, using methods that are known in the art of antibody production. Thus, the present
invention also includes antibodies to human BMP-17 and/or BMP-18 and/or other related proteins. The
antibodies may be useful for purification of BMP-17 and/or BMP-18 and/or other BMP-17 and/or BMP-18
related proteins, or for inhibiting or preventing the effects of BMP-17 and/or BMP-18 related
proteins. The BMP-17 and/or BMP-18 protein and related proteins may be useful for inducing the
growth and/or differentiation of embryonic cells and/or stem cells. Thus, the proteins or
compositions of the present invention may also be useful for treating relatively undifferentiated
cell populations, such as embryonic cells or stem cell populations, to enhance or enrich the growth
and/or differentiation of the cells. The treated cell populations may be useful for implantation and
for gene therapy applications.

BSPR:
The BMP-17 or BMP-18 proteins recovered from the culture medium are purified by isolating them from
other proteinaceous materials from which they are co-produced and from other contaminants present.
BMP-17 or BMP-18 proteins may be characterized by the ability to induce the formation of cartilage
and/or bone and/or other connective tissue and other tissue repair and differentiation, for example,
in the rat bone formation assay described below. In addition, BMP-17 or BMP-18 proteins may be
further characterized by their effects upon the growth and/or differentiation of embryonic cells
and/or stem cells. Thus, the proteins or compositions of the present invention may be characterized
by the embryonic stem cell assay described below.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, MA. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

DEPR:
In order to assay the effects of the BMP-17 and BMP-18 proteins of the present invention, it is
possible to assay the growth and differentiation effects in vitro on a number of available embryonic
stem cell lines. One such cell line is ES-E14TG2, which is available from the American Type Culture
Collection in Rockville, Md.

19. Document ID: US 6022887 A

L7: Entry 19 of 46

File: USPT

Feb 8, 2000

US-PAT-NO: 6022887
DOCUMENT-IDENTIFIER: US 6022887 A
TITLE: Compositions and methods for stimulating bone growth
DATE-ISSUED: February 8, 2000

US-CL-CURRENT: 514/451; 514/460, 549/273

APPL-NO: 8/ 989862
DATE FILED: December 12, 1997

PARENT-CASE:
This application claims priority under 35 USC 119 from provisional application Ser. No. 60/032,893
filed Dec. 31, 1996, the entire contents of which are incorporated herein by reference.

IN: Gasper; Shirley R., West; Robert R., Martinez; Theresa, Robbins; Kirk G., McKernan;
Patricia A., Baindur; Nand, Labroo; Virender M.

AB: Compounds of the formula ##STR1## wherein X in each of formulas (1) and (2)
represents a substituted or unsubstituted alkylene, alkenylene, or alkynylene linker of 2-6C;,
Y represents one or more carbocyclic or heterocyclic rings; when two or more rings are present
in Y, they may optionally be fused; and, R' represents a cation, H or a substituted or
unsubstituted alkyl group of 1-6C; and, the dotted lines represent optional .pi.-bonds,,
promote bone formation and are thus usefull in treating osteoporosis, bone fracture or
deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic
bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and
post-dental implantation.

L7: Entry 19 of 46

File: USPT

Feb 8, 2000

DOCUMENT-IDENTIFIER: US 6022887 A
TITLE: Compositions and methods for stimulating bone growth

ORPL:
Rickard, D.J., et al., "Induction of Rapid Osteoblast Differentiation in Rat Bone Marrow Stromal
Cell Cultures by Dexamethasone and BMP-2," Developmental Biology 161:218-228 (Jan. 1994).

20. Document ID: US 6008188 A

L7: Entry 20 of 46

File: USPT

Dec 28, 1999

US-PAT-NO: 6008188
DOCUMENT-IDENTIFIER: US 6008188 A
TITLE: Cytokine potentiator and pharmaceutical formulation for cytokine administration

DATE-ISSUED: December 28, 1999

US-CL-CURRENT: 514/2; 424/85.1, 424/85.2, 424/85.4, 514/561, 514/667, 514/669, 514/673, 562/567, 564/503

APPL-NO: 8/ 737064
DATE FILED: December 16, 1996

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	6-117495	May 6, 1994

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/JP95/00857	April 28, 1995	WO95/30412	Nov 16, 1995	Dec 16, 1996	Dec 16, 1996

IN: Oishi; Yuichi, Yoshida; Masaki, Inoue; Shintaro

AB: A cytokine activity enhancer comprising an ethanolamine derivative of the following general formula (I) or a salt thereof, or comprising it along with cytokine or a cytokine production promoter; and also a medicine for diseases with lowered cytokine activity, comprising, as the active ingredient, the cytokine activity enhancer: ##STR1## wherein R.sub.1 is H, --CH.sub.3, --CH.sub.2 CH(CH.sub.3)OH or --CH.sub.2 CH.sub.2 OH; R.sub.2 is H, --CH.sub.3, --CH.sub.2 CH.sub.3 or --COOH; and R.sub.3 is H, --CH.sub.3, --CH.sub.2 CH.sub.3 or --CH.sub.2 NH.sub.2.

L7: Entry 20 of 46
File: USPT
Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6008188 A
TITLE: Cytokine potentiator and pharmaceutical formulation for cytokine administration

DEPR:
Cytokines as referred to herein include platelet-derived growth factor (hereinafter referred to as PDGF), fibroblast growth factor (hereinafter referred to as FGF), epidermal growth factor (hereinafter referred to as EGF), transforming growth factor (hereinafter referred to as TGF), bone morphogenetic protein (hereinafter referred to as BMP), interferon (hereinafter referred to as IFN), granulocyte colony-stimulating factor (hereinafter referred to as G-CSF), macrophage colony-stimulating factor (hereinafter referred to as M-CSF), insulin-like growth factor (hereinafter referred to as IGF), hepatocyte growth factor (hereinafter referred to as HGF), stem cell factor (hereinafter referred to as SCF), nerve growth factor (hereinafter referred to as NGF), vascular endothelial cell growth factor (hereinafter referred to as VEGF), keratinocyte growth factor (hereinafter referred to as KGF), interleukin (see Interleukin Network, Kodan-sha, 1992, the entirety of which is herein incorporated by reference), and the like. Of these cytokines, those which activate tyrosine or serine/threonine kinases, and also activate the phosphorylation of tyrosine, or serine and/or threonine residues on subunits of tyrosine or serine/threonine kinase-linked receptors, respectively, are preferred effectors.

21. Document ID: US 5986056 A

L7: Entry 21 of 46
File: USPT
Nov 16, 1999

US-PAT-NO: 5986056
DOCUMENT-IDENTIFIER: US 5986056 A
TITLE: Chordin compositions
DATE-ISSUED: November 16, 1999

US-CL-CURRENT: 530/350; 435/69.1

APPL-NO: 9/ 130032
DATE FILED: August 4, 1998

PARENT-CASE:
This application is a divisional of U.S. Ser. No. 08/749,169, U.S. Pat. No. 5,846,770 filed Nov. 14, 1996, which application is a continuation-in-part of U.S. Ser. No. 08/343,760, filed Nov. 22, 1994, and now issued as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA molecules encoding the chordin proteins are also disclosed. The proteins may be used in the treatment of bone, cartilage, other connective tissue defects and disorders, including tendon, ligament and meniscus, in wound healing and related tissue repair, as well for treatment of disorders and defects to tissue which include epidermis, nerve, muscle, including cardiac muscle, and othe tissues and wounds, and organs such as liver, brain, lung, cardiac, pancreas and kidney tissue. The proteins may also be useful for the induction inhibition of growth and/or differentiation of undifferentiated embryonic and stem cells. The proteins may be complexed with other proteins, particularly members of the transforming growth factor-beta superfamily of proteins.

L7: Entry 21 of 46
File: USPT
Nov 16, 1999

DOCUMENT-IDENTIFIER: US 5986056 A
TITLE: Chordin compositions

BSPR:
The chordin proteins of the present invention, include polypeptides having a molecular weight of

about 105-110 kd, said polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having the
ability to bind to TGF-.beta. and/or BMP proteins, or the ability to alter or influence the
formation of cartilage and/or bone and/or other connective tissues, such as exhibited in the
embryonic stem cell and Rosen-Modified Sampath-Reddi ectopic implant assays, described in the
examples.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

22. Document ID: US 5976523 A

L7: Entry 22 of 46 File: USPT Nov 2, 1999

US-PAT-NO: 5976523
DOCUMENT-IDENTIFIER: US 5976523 A
TITLE: Method for healing compromised tissues using pyrimidine derivatives
DATE-ISSUED: November 2, 1999

US-CL-CURRENT: 424/85.1; 514/228.5, 514/234.2, 514/252.16, 514/258, 530/300, 530/350

APPL-NO: 8/ 656158
DATE FILED: May 16, 1996

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	7-141074	May 16, 1995
JP	8-071329	March 2, 1996

IN: Awaya; Akira, Ito; Fumiaki, Torigoe; Kojun, Tomino; Ikuo

AB: The present invention provides a method for the screening of a wound-healing agent,
which comprises determining a substance to be active as a wound-healing agent on the basis of
potentiation or modification of biological activities of a growth and/or differentiation
factor, a growth hormone or a cytokine. This invention also provides a wound-healing method,
which comprises as an active ingredient a compound of the following formula (1) or formula (2)
found to be active by the screening method. ##STR1##

L7: Entry 22 of 46 File: USPT Nov 2, 1999

DOCUMENT-IDENTIFIER: US 5976523 A
TITLE: Method for healing compromised tissues using pyrimidine derivatives

CLPR:
7. A method according to claim 3, wherein said biological activities are activities of at least one
biological substance selected from the group consisting of an epidermal growth factor (EGF), an
acidic fibroblast growth factor (aFGF), a basic fibroblast growth factor (bFGF), an .alpha. or
.beta. transforming growth factor (TGF), a vascular endothelial cell growth factor (VEGF), a
platelet-derived growth factor (PDGF), a platelet-derived endothelial cell growth factor (PDECGF), a
bone morphogenic protein (BMP), a hepatocyte growth factor (HGF), midkine, a tumor necrosis factor
(TNF), insulin, an insulin-like growth factor (IGF-I, II), a keratinocyte growth factor, an
endothelial cell growth factor (ECGF), a fibroblast-derived epithelial cell growth factor, a
granulocyte-colony stimulating factor (G-CSF), a macrophage-colony stimulating factor (M-CSF), a
granulocyte-macrophage-colonystimulating factor (GM-CSF), thrombopoietin (TPO), a leukemia
inhibitory factor (LIF), a stem cell factor (SCF), erythropoietin (EPO), an adult T cell
leukemia-derived factor (ADF), macrophage inflammatory protein 1.alpha.(MIP-1.alpha.), transferrin,
thrombin, thrombomodulin, interleukin-1 (IL-1), interleukin- (IL4), interleukin-6 (IL-6),
interleukin-8 (IL-8), a heparin releasing factor (HRF), a monocyte chemotactic activator, a
calcitonin gene related peptide (CGRP), superoxide dismutase (SOD), an angiotensin, a prostaglandin,
serotonin, collagen, fibronectin, laminin and a homologue of any of the foregoing..

23. Document ID: US 5972368 A

L7: Entry 23 of 46 File: USPT Oct 26, 1999

US-PAT-NO: 5972368
DOCUMENT-IDENTIFIER: US 5972368 A
TITLE: Bone graft composites and spacers
DATE-ISSUED: October 26, 1999

US-CL-CURRENT: 424/423; 424/422, 424/426, 514/2, 530/840

APPL-NO: 8/ 873276
DATE FILED: June 11, 1997

IN: McKay; William F.

AB: A bone graft substitute including a composition of natural selectively deactivated
bone material which has been processed to remove associated non-collagenous bone proteins, said
bone material containing native collagen materials and naturally associated bone minerals and
substantially free from native non-collagenous protein, and a therapeutically effective amount
to stimulate bone growth of a bone growth factor in a pharmaceutically acceptable carrier in
synergistic combination with said bone material. Spacers composed of the bone graft substitute
composition methods for using the spacers are also provided.

L7: Entry 23 of 46

File: USPT

Oct 26, 1999

DOCUMENT-IDENTIFIER: US 5972368 A
TITLE: Bone graft composites and spacers

DRPR:
This invention provides the further advantage of exploiting the discovery that bone mineral is an
excellent carrier for osteogenic factors such as bone morphogenic proteins. Hydroxyapatite which is
very similar in chemical composition to the mineral in cortical bone is an osteogenic factor-binding
agent which controls the rate of delivery of certain proteins to the fusion site. Calcium phosphate
compositions such as hydroxyapatite are thought to bind bone morphogenic proteins and prevent BMP
from prematurely dissipating from the spacer before fusion can occur. It is further believed that
retention of the BMP by the agent permits the protein to initiate the transformation of mesenchymal
stem cells into bone producing cells or osteoblasts within the device at a rate that is conducive to
complete and rapid bone formation and ultimately, fusion across the disc space. The spacers of this
invention have the advantage of including a load bearing member composed of selectively deactivated
bone which naturally binds and provides controlled delivery of osteogenic factors such as bone
morphogenic proteins.

24. Document ID: US 5965403 A

L7: Entry 24 of 46

File: USPT

Oct 12, 1999

US-PAT-NO: 5965403
DOCUMENT-IDENTIFIER: US 5965403 A
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)
DATE-ISSUED: October 12, 1999

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/69.1, 435/69.7, 536/23.1, 536/23.5,
536/23.51, 536/24.1

APPL-NO: 8/ 715202
DATE FILED: September 18, 1996

IN: Celeste; Anthony J., Murray; Beth L.

AB: Purified BMP-16 proteins and processes for producing them are disclosed. DNA
molecules encoding the BMP-16 proteins are also disclosed. The proteins may be used in the
treatment of bone, cartilage, other connective tissue defects and disorders, including tendon,
ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of
disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac
muscle, and other tissues and wounds, and organs such as liver, lung, cardiac, pancreas and
kidney tissue. The proteins may also be useful for the induction of growth and/or
differentiation of undifferentiated embryonic and stem cells.

L7: Entry 24 of 46

File: USPT

Oct 12, 1999

DOCUMENT-IDENTIFIER: US 5965403 A
TITLE: Nucleic acids encoding bone morphogenic protein-16 (BMP-16)

BSPR:
The BMP-16 DNA sequence (SEQ ID NO: 1) and amino acid sequence (SEQ ID NO: 2) are set forth in the
Sequence Listings. BMP-16 proteins may be capable of inducing the formation of cartilage, bone, or
other connective tissue, or combinations thereof. The cartilage and/or bone and/or other connective
tissue formation activity in the rat bone formation assay described below. BMP-16 proteins may be
further characterized by the ability to demonstrate effects upon the growth and/or differentiation
of embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention
may also be useful for treating cell populations, such as embryonic cells or stem cell populations,
to enhance or enrich the growth and/or differentiation of the cells.

BSPR:
It is expected that other species, particularly human, have DNA sequences homologous to human BMP-16
protein. The invention, therefore, includes methods for obtaining the DNA sequences encoding human
BMP-16 protein, the DNA sequences obtained by those methods, and the human protein encoded by those
DNA sequences. This method entails utilizing the human BMP-16 protein nucleotide sequence or
portions thereof to design probes to screen libraries for the corresponding gene from other species
or coding sequences or fragments thereof from using standard techniques. Thus, the present invention
may include DNA sequences from other species, which are homologous to human BMP-16 protein and can
be obtained using the human BMP-16 sequence. The present invention may also include functional
fragments of the human BMP-16 protein, and DNA sequences encoding such functional fragments, as well
as functional fragments of other related proteins. The ability of such a fragment to function is
determinable by assay of the protein in the biological assays described for the assay of the BMP-16
protein. A DNA sequence encoding the complete mature human BMP-16 protein (SEQ ID NO:1) and the
corresponding amino acid sequence (SEQ ID NO:2) are set forth herein. The BMP-16 proteins of the
present invention, such as human BMP-16, may be produced by culturing a cell transformed with the
correlating DNA sequence, such as the human BMP-16 DNA sequence, and recovering and purifying
protein, such as BMP-16, from the culture medium. The purified expressed protein is substantially
free from other proteinaceous materials with which it is co-produced, as well as from other

contaminants. The recovered purified protein is contemplated to exhibit cartilage and/or bone and/or
connective tissue formation activity. Thus, the proteins of the invention may be further
characterized by the ability to demonstrate cartilage and/or bone and/or other connective tissue
formation activity in the rat bone formation assay described below. BMP-16 proteins may be further
characterized by the ability to demonstrate effects upon the growth and/or differentiation of
embryonic cells and/or stem cells. Thus, the proteins or compositions of the present invention may
also be characterized by their ability to enhance or enrich the growth and/or differentiation of the
cells.

BSPR:
The purified proteins of the present inventions may be used to generate antibodies, either
monoclonal or polyclonal, to human BMP-16 and/or other BMP-16-related proteins, using methods that
are known in the art of antibody production. Thus, the present invention also includes antibodies to
human BMP-16 and/or other related proteins. The antibodies may be useful for purification of BMP-16
and/or other BMP-16 related proteins, or for inhibiting or preventing the effects of BMP-16 related
proteins. The BMP-16 protein and related proteins may be useful for inducing the growth and/or
differentiation of embryonic cells and/or stem cells. Thus, the proteins or compositions of the
present invention may also be useful for treating relatively undifferentiated cell populations, such
as embryonic cells or stem cell populations, to enhance or enrich the growth and/or differentiation
of the cells. The treated cell populations may be useful for implantation and for gene therapy
applications.

BSPR:
The BMP-16 proteins recovered from the culture medium are purified by isolating them from other
proteinaceous materials from which they are co-produced and from other contaminants present. BMP-16
proteins may be characterized by the ability to induce the formation of cartilage and/or bone and/or
other connective tissue and other tissue repair and differentiation, for example, in the rat bone
formation assay described below. In addition, BMP-16 proteins may be further characterized by their
effects upon the growth and/or differentiation of embryonic cells and/or stem cells. Thus, the
proteins or compositions of the present invention may be characterized by the embryonic stem cell
assay described below.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

DEPR:
In order to assay the effects of the BMP-16 proteins of the present invention, it is possible to
assay the growth and differentiation effects in vitro on a number of available embryonic stem cell
lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection
10801 University Boulevard, Manassas, Va. 20110-2209.

25. Document ID: US 5942225 A

L7: Entry 25 of 46

File: USPT

Aug 24, 1999

US-PAT-NO: 5942225
DOCUMENT-IDENTIFIER: US 5942225 A
TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation
DATE-ISSUED: August 24, 1999

US-CL-CURRENT: 424/93.7; 435/366, 435/372

APPL-NO: 8/ 899414
DATE FILED: July 23, 1997

PARENT-CASE:
This application is a divisional of U.S. application Ser. No. 08/377,461 filed Jan. 24, 1995, now
U.S. Pat. No. 5,736,396.

IN: Bruder; Scott P., Caplan; Arnold I., Haynesworth; Stephen E.

AB: Methods for in vitro or ex vivo lineage directed induction of isolated, culture
expanded human mesenchymal stem cells comprising contacting the mesenchymal stem cells with a
bioactive factor effective to induce differentiation thereof into a lineage of choice as well
as such compositions including isolated culture expanded human mesenchymal stem cells and
bioactive factors effective to induce directed lineage induction are disclosed. Further
disclosed is this method which also includes introducing such culturally expanded
lineage-induced mesenchymal stem cells into a host from which they have originated for purposes
of mesenchymal tissue regeneration or repair.

L7: Entry 25 of 46

File: USPT

Aug 24, 1999

DOCUMENT-IDENTIFIER: US 5942225 A
TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

DEPR:
Factors which stimulate osteogenesis (i.e. are osteoinductive) from isolated human mesenchymal stem
cells in accordance with the invention are present in several classes of molecules, including the
following: bone morphogenic proteins, such as BMP-2 (14) and BMP-3 (15); growth factors, such as

basic fibroblast growth factor (bFGF); glucocorticoids, such as dexamethasone (16); and
prostaglandins, such as prostaglandin E1 (22). Further, ascorbic acid and its analogs, such as
ascorbic acid-2-phosphate (17) and glycerol phosphates, such as .beta.-glycerophosphate (18) are
effective adjunct factors for advanced differentiation, although alone they do not induce osteogenic
differentiation.

26. Document ID: US 5939388 A

L7: Entry 26 of 46

File: USPT

Aug 17, 1999

US-PAT-NO: 5939388
DOCUMENT-IDENTIFIER: US 5939388 A
TITLE: Methods of administering BMP-5 compositions
DATE-ISSUED: August 17, 1999

US-CL-CURRENT: 514/12; 424/85.1, 514/2

APPL-NO: 8/ 788729
DATE FILED: January 23, 1997

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No.
08/469,935, filed Jun. 6, 1995, now U.S. Pat. No. 5,635,373, which is a divisional of U.S. Ser. No.
08/116,425, filed Sep. 7, 1993, now U.S. Pat. No. 5,543,394, which is a continuation of U.S. Ser.
No. 07/995,565, filed Dec. 22, 1992, now abandoned, which is a continuation of U.S. Ser.
No.07/588,227, filed Sep. 26, 1990, now abandoned, which is a continuation-in-part of U.S. Ser. No.
07/437,409, filed Nov. 15, 1989, now abandoned; which is a continuation-in-part of U.S. Ser. No.
07/370,547, filed Jun. 23, 1989, now U.S. Pat. No. 5,106,748; which is a continuation-in-part of
U.S. Ser. No. 07/347,559, filed May 4, 1989, now abandoned; which is a continuation-in-part of U.S.
Ser. No. 07/329,610, filed Mar. 28, 1989, now abandoned, which is a continuation-in-part of U.S.
Ser. No. 07/179,100, now U.S. Pat. No. 5,013,649, U.S. Ser. No. 07/179,101, now abandoned, and U.S.
Ser. No. 07/179,197, now abandoned; each filed Apr. 8, 1988, which are continuations-in-part of U.S.
Ser. No. 07/028,285, filed Mar. 20, 1987, now abandoned, and U.S. Ser. No. 07/031,346, filed Mar.
26, 1987, now U.S. Pat. No. 4,877,864, which are continuations-in-part of U.S. Ser. No. 06/943,332,
filed Dec. 17, 1986, now abandoned, and Ser. No. 06/880,776, filed Jul. 1, 1986, now abandoned.

IN: Rosen; Vicki A., Wozney; John M., Wang; Elizabeth A.

AB: Purified BMP-5 proteins and processes for producing them are disclosed. The proteins
may be used in the treatment of bone and/or cartilage defects and in wound healing and related
tissue repair.

L7: Entry 26 of 46

File: USPT

Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5939388 A
TITLE: Methods of administering BMP-5 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

DEPR:
In order to assay the effects of the BMP-5 proteins of the present invention, it is possible to
assay the growth and differentiation effects in vitro on a number of available embryonic stem cell
lines. One such cell line is ES-E14TG2, which is available from the American Type Culture Collection
in Rockville, Md.

27. Document ID: US 5939323 A

L7: Entry 27 of 46

File: USPT

Aug 17, 1999

US-PAT-NO: 5939323
DOCUMENT-IDENTIFIER: US 5939323 A
TITLE: Hyaluronan based biodegradable scaffolds for tissue repair
DATE-ISSUED: August 17, 1999

US-CL-CURRENT: 435/395; 424/426

APPL-NO: 8/ 864709
DATE FILED: May 28, 1997

PARENT-CASE:
RELATED APPLICATIONS This application claims priority under 35 USC .sctn. 119(e) from U.S.
provisional patent application Ser. No. 60/018,492 filed on May 28, 1996, entitled Hyaluronan Based
Biodegradable Scaffolds for Tissue Repair. The contents of the provisional application are hereby
expressly incorporated by reference.

IN: Valentini; Robert F., Kim; Hyun D.

AB: A hyaluronic acid derivitized scaffold and method of forming are disclosed. The
scaffolds are useful for various medical purposes such as tissue repair, tissue reconstruction
and wound healing. In order to enhance these processes the scaffolds may

be engineered to
incorporate biologically active molecules such as BMP.

L7: Entry 27 of 46
File: USPT
Aug 17, 1999

DOCUMENT-IDENTIFIER: US 5939323 A
TITLE: Hyaluronan based biodegradable scaffolds for tissue repair

DEPR:
3. BMP Release Bioassay by Alkaline Phosphatase (AP) Induction of Pluripotent Stem Cells

from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

28. Document ID: US 5932216 A

L7: Entry 28 of 46
File: USPT
Aug 3, 1999

US-PAT-NO: 5932216
DOCUMENT-IDENTIFIER: US 5932216 A
TITLE: Antibodies to bone morphogenetic protein-10 (BMP-10)
DATE-ISSUED: August 3, 1999

US-CL-CURRENT: 424/158.1; 424/139.1

APPL-NO: 8/ 926885
DATE FILED: September 10, 1997

PARENT-CASE:
This application is a continuation of application Ser. No. 453,942, filed May 30, 1995, U.S. Pat.
No. 5,703,043, which is a divisional of Ser. No. 08/247,908 filed May 20, 1994 (issued Jun. 10, 1994
as U.S. Pat. No. 5,637,480); which is a continuation-in-part of Ser. No. 08/061,695 filed May 12,
1993 (abandoned).

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10(BMP-10) proteins and processes for producing
them are disclosed. DNA molecules encoding the BMP-10 proteins are also disclosed. The proteins
may be used in the treatment of bone and cartilage defects and in wound healing and related
tissue repair.

L7: Entry 28 of 46
File: USPT
Aug 3, 1999

DOCUMENT-IDENTIFIER: US 5932216 A
TITLE: Antibodies to bone morphogenetic protein-10 (BMP-10)

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived

29. Document ID: US 5866364 A

L7: Entry 29 of 46
File: USPT
Feb 2, 1999

US-PAT-NO: 5866364
DOCUMENT-IDENTIFIER: US 5866364 A
TITLE: Recombinant bone morphogenetic protein heterodimers
DATE-ISSUED: February 2, 1999

US-CL-CURRENT: 435/69.1; 435/252.3, 435/252.33, 435/255.1, 435/320.1, 435/325, 435/70.2, 530/350,
530/399, 536/23.5

APPL-NO: 7/ 989847
DATE FILED: November 27, 1992

PARENT-CASE:
CROSS REFERENCE TO RELATED APPLICATIONS This application is a continuation-in-part of U.S. Ser. No.
07/864,692 filed Apr. 7, 1992, now abandoned which is a continuation-in-part of U.S. Ser. No.
07/787,496 filed Nov. 4, 1991 now abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY APPL-NO APPL-DATE
WO PCT/US92/09430 November 2, 1992

IN: Israel; David, Wolfman; Neil M.

AB: The present invention relates to a methods for producing recombinant heterodimeric
BMP proteins useful in the field of treating bone defects, healing bone injury and in wound
healing in general. The invention also relates to the recombinant heterodimers and compositions
containing them.

L7: Entry 29 of 46
File: USPT
Feb 2, 1999

DOCUMENT-IDENTIFIER: US 5866364 A
TITLE: Recombinant bone morphogenetic protein heterodimers

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with BMP-2 [R. S. Thies et al, "Bone
Morphogenetic Protein alters W-20 stromal cell differentiation in vitro", Journal of Bone and
Mineral Research, 5(2):305 (1990); and R. S. Thies et al, "Recombinant Human Bone Morphogenetic
Protein 2 Induces Osteoblastic Differentiation in W-20-17 Stromal Cells", Endocrinology, in press
(1992)]. Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice
by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. BMP-2
treatment of W-20 cells results in (1) increased alkaline phosphatase production, (2) induction of
PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2)
represent characteristics associated with the osteoblast phenotype, the ability to synthesize
osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we
have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with
BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the
in vivo bone forming activity known for BMPs.

30. Document ID: US 5846770 A

L7: Entry 30 of 46

File: USPT

Dec 8, 1998

US-PAT-NO: 5846770
DOCUMENT-IDENTIFIER: US 5846770 A
TITLE: DNA molecules encoding human chordin
DATE-ISSUED: December 8, 1998

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/69.7, 536/23.4, 536/23.5

APPL-NO: 8/ 749169
DATE FILED: November 14, 1996

PARENT-CASE:
This application is a continuation-in-part from Ser. No. 343,760, filed on Nov. 22, 1994, and issued
as U.S. Pat. No. 5,679,783.

IN: LaVallie; Edward R., Racie; Lisa A., DeRobertis; Edward M.

AB: Purified chordin proteins and processes for producing them are disclosed. DNA
molecules encoding the chordin proteins are also disclosed. The proteins may be used in the
treatment of bone, cartilage, other connective tissue defects and disorders, including tendon,
ligament and meniscus, in wound healing and related tissue repair, as well as for treatment of
disorders and defects to tissues which include epidermis, nerve, muscle, including cardiac
muscle, and other tissues and wounds, and organs such as liver, brain, lung, cardiac, pancreas
and kidney tissue. The proteins may also be useful for the induction inhibition of growth
and/or differentiation of undifferentiated embryonic and stem cells. The proteins may be
complexed with other proteins, particularly members of the transforming growth factor-beta
superfamily of proteins.

L7: Entry 30 of 46

File: USPT

Dec 8, 1998

DOCUMENT-IDENTIFIER: US 5846770 A
TITLE: DNA molecules encoding human chordin

BSPR:
The chordin proteins of the present invention, include polypeptides having a molecular weight of
about 105-110 kd, said polypeptide comprising the amino acid sequence of SEQ ID NO: 3 and having the
ability to bind to TGF-.beta. and/or BMP proteins, or the ability to alter or influence the
formation of cartilage and/or bone and/or other connective tissues, such as exhibited in the
embryonic stem cell and Rosen-Modified Sampath-Reddi ectopic implant assays, described in the
examples.

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5: 305 (1990); and Thies et al, Endocrinology, 130: 1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

31. Document ID: US 5804416 A

L7: Entry 31 of 46

File: USPT

Sep 8, 1998

US-PAT-NO: 5804416
DOCUMENT-IDENTIFIER: US 5804416 A
TITLE: Mutants of bone morphogenetic proteins
DATE-ISSUED: September 8, 1998

US-CL-CURRENT: 435/69.1; 530/333, 530/350, 530/399

APPL-NO: 8/ 741589
DATE FILED: October 31, 1996

PARENT-CASE:
This application is a divisional of application Ser. No. 08/360,914, filed Dec. 21, 1994, which has
issued as U.S. Pat. No. 5,756,308 which application is a

continuation-in-part of PCT application
PCT/US94/13181, filed on Nov. 15, 1994, which is a continuation-in-part of application Ser. No.
08/163,877, filed on Dec. 7, 1993, which has issued as U.S. Pat. No. 5,399,677.

IN: Wolfman; Neil M., McCoy; John

AB: DNA molecules encoding mutant forms of bone morphogenetic proteins (BMP) are
disclosed. The mutant forms of BMP can be produced bacterially and refolded to produce
biologically active homodimers or heterodimers of BMP. A method of making such mutant BMPs is
also disclosed.

L7: Entry 31 of 46

File: USPT

Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804416 A
TITLE: Mutants of bone morphogenetic proteins

DEPR:
The in vitro biological activity of the refolded bone morphogenetic proteins is monitored by the
W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow stromal cells as an indicator
cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with
BMP [R. S. Thies et al., Journal of Bone and Mineral Research 5(2):305 (1990); and R. S. Thies et
al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal bone marrow stromal cell line
derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,
Boston, Mass. Treatment of W-20-17 cells with BMP results in (1) increased alkaline phosphatase
production, (2) induction of parathyroid hormone stimulated cAMP, and (3) induction of osteocalcin
synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast
phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature
osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells to osteoblast-like cells
has been observed only upon treatment with bone morphogenetic proteins. The in vivo biological
activity of the refolded bone morphogenetic proteins is monitored by a modified version of the rat
bone formation assay described in Sampath and Reddi, Proc. Natl. Acad. Sci. USA, 80:6591-6595 (1983)
herein called the Rosen-modified Sampath-Reddi assay, as set forth in Example 10.

32. Document ID: US 5756457 A

L7: Entry 32 of 46

File: USPT

May 26, 1998

US-PAT-NO: 5756457
DOCUMENT-IDENTIFIER: US 5756457 A
TITLE: Neural regeneration using human bone morphogenetic proteins
DATE-ISSUED: May 26, 1998

US-CL-CURRENT: 514/12; 424/422, 424/423, 606/152

APPL-NO: 8/ 435120
DATE FILED: May 5, 1995

PARENT-CASE:
RELATED APPLICATIONS The present application is a continuation-in-part of Ser. No. 08/112,492, filed
on Aug. 26, 1993, which has been abandoned.

IN: Wang; Elizabeth A., D'Alessandro; Josephine S., Toriumi; Dean M.

AB: Methods and devices are disclosed for inducing growth of neural cells, and repairing
neural defects in a mammal. The method comprises administering to said mammal at the site of
neural defect, damage or depletion, an effective amount of a bone morphogenetic protein, either
in admixture with a pharmaceutically acceptable vehicle, or adsorbed to a suitable matrix. The
device comprises bone morphogenetic protein, optionally in combination with other factors,
adsorbed on a suitable matrix and contained within an artificial nerve replacement vessel.

L7: Entry 32 of 46

File: USPT

May 26, 1998

DOCUMENT-IDENTIFIER: US 5756457 A
TITLE: Neural regeneration using human bone morphogenetic proteins

BSPR:
In accordance with the method of the invention, BMP, such as rhBMP-2, may be administered alone, in
combination with other BMPs, or in combination with other therapies. For example, rhBMP-2 may be
efficaciously combined with a cytokine, lymphokine, growth factor, or colony stimulating factor, in
the treatment of neural diseases. Exemplary cytokines, lymphokines, growth factors, and colony
stimulating factors for use in combination with BMP in accordance with the method of the invention
include, without limitation, EGF, FGF, interleukins 1 through 12, M-CSF, G-CSF, GM-CSF, stem cell
factor, erythropoietin, and the like. In addition, the BMPs may be combined with neurotrophic
factors such as CNTF, LIF, IL-6 and insulin-like growth factors [IGFs]. Additionally, proteins
normally found in the neural environment may be added to the BMPs in accordance with the present
invention. These may include laminin, hyalauronic acid and chondroitin sulfate proteoglycans,
including versican.

33. Document ID: US 5756308 A

L7: Entry 33 of 46

File: USPT

May 26, 1998

US-PAT-NO: 5756308
DOCUMENT-IDENTIFIER: US 5756308 A
TITLE: Refolding variant of bone morphogenetic protein-8
DATE-ISSUED: May 26, 1998

US-CL-CURRENT: 435/69.1; 530/333, 530/399, 536/23.5

APPL-NO: 8/ 360914
DATE FILED: December 21, 1994

PARENT-CASE:
The present application is a continuation-in-part of Ser. No. 08/163,877, filed on Dec. 7, 1993,
which has issued as U.S. Pat. No. 5,399,677, and claims priority from PCT application Ser. No.
PCT/US94/13181, filed on Nov. 15, 1994.

IN: Wolfman; Neil M., McCoy; John

AB: DNA molecules encoding mutant forms of bone morphogenetic proteins (BMP) are
disclosed. The mutant forms of BMP can be produced bacterially and refolded to produce
biologically active homodimers or heterodimers of BMP. A method of making such mutant BMPs is
also disclosed.

L7: Entry 33 of 46
File: USPT
May 26, 1998

DOCUMENT-IDENTIFIER: US 5756308 A
TITLE: Refolding variant of bone morphogenetic protein-8

DEPR:
The in vitro biological activity of the refolded bone morphogenetic proteins is monitored by the
W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow stromal cells as an indicator
cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with
BMP [R. S. Thies et al., Journal of Bone and Mineral Research 5(2):305 (1990); and R. S. Thies et
al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal bone marrow stromal cell line
derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital,
Boston, MA. Treatment of W-20-17 cells with BMP results in (1) increased alkaline phosphatase
production, (2) induction of parathyroid hormone stimulated cAMP, and (3) induction of osteocalcin
synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast
phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature
osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells to osteoblast-like cells
has been observed only upon treatment with bone morphogenetic proteins. The in vivo biological
activity of the refolded bone morphogenetic proteins is monitored by a modified version of the rat
bone formation assay described in Sampath and Reddi, Proc. Natl. Acad. Sci. USA, 80:6591-6595 (1983)
herein called the Rosen-modified Sampath-Reddi assay, as set forth in Example 10.

34. Document ID: US 5736396 A

L7: Entry 34 of 46
File: USPT
Apr 7, 1998

US-PAT-NO: 5736396
DOCUMENT-IDENTIFIER: US 5736396 A
TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation
DATE-ISSUED: April 7, 1998

US-CL-CURRENT: 435/366; 424/93.7, 435/372

APPL-NO: 8/ 377461
DATE FILED: January 24, 1995

IN: Bruder; Scott P., Caplan; Arnold I., Haynesworth; Stephen E.

AB: Methods for in vitro or ex vivo lineage directed induction of isolated, culture
expanded human mesenchymal stem cells comprising contacting the mesenchymal stem cells with a
bioactive factor effective to induce differentiation thereof into a lineage of choice as well
as such compositions including isolated culture expanded human mesenchymal stem cells and
bioactive factors effective to induce directed lineage induction are disclosed. Further
disclosed is this method which also includes introducing such culturally expanded
lineage-induced mesenchymal stem cells into a host from which they have originated for purposes
of mesenchymal tissue regeneration or repair.

L7: Entry 34 of 46
File: USPT
Apr 7, 1998

DOCUMENT-IDENTIFIER: US 5736396 A
TITLE: Lineage-directed induction of human mesenchymal stem cell differentiation

DEPR:
Factors which stimulate osteogenesis (i.e. are osteoinductive) from isolated human mesenchymal stem
cells in accordance with the invention are present in several classes of molecules, including the
following: bone morphogenic proteins, such as BMP-2 (14) and BMP-3 (15); growth factors, such as
basic fibroblast growth factor (bFGF); glucocorticoids, such as dexamethasone (16); and
prostaglandins, such as prostaglandin E1 (22). Further, ascorbic acid and its analogs, such as
ascorbic acid-2-phosphate (17) and glycerol phosphates, such as .beta.-glycerophosphate (18) are
effective adjunct factors for advanced differentiation, although alone they do not induce osteogenic
differentiation.

35. Document ID: US 5728679 A

L7: Entry 35 of 46
File: USPT
Mar 17, 1998

US-PAT-NO: 5728679
DOCUMENT-IDENTIFIER: US 5728679 A
TITLE: BMP-15 compositions
DATE-ISSUED: March 17, 1998

US-CL-CURRENT: 514/12; 424/484, 530/350, 530/387.1, 530/395, 530/399

APPL-NO: 8/ 798665

DATE FILED: February 11, 1997

PARENT-CASE:
This application is a division of application Ser. No. 08/446,924, filed May 18, 1995 now U.S. Pat.
No. 5,635,372.

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA
molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in
the treatment of bone and cartilage and/or other connective tissue defects and in wound healing
and related tissue repair.

L7: Entry 35 of 46

File: USPT

Mar 17, 1998

DOCUMENT-IDENTIFIER: US 5728679 A
TITLE: BMP-15 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (19.90); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

36. Document ID: US 5703043 A

L7: Entry 36 of 46

File: USPT

Dec 30, 1997

US-PAT-NO: 5703043
DOCUMENT-IDENTIFIER: US 5703043 A
TITLE: Bone morphogenetic protein-10 (BMP-10) compositions
DATE-ISSUED: December 30, 1997

US-CL-CURRENT: 514/12; 435/69.1, 530/399, 536/23.5, 930/120

APPL-NO: 8/ 453942
DATE FILED: May 30, 1995

PARENT-CASE:
This application is a Divisional of U.S. Ser. No. 08/247,908, filed as PCT/US94/05290 May 12, 1994,
U.S. Pat. No. 5,637,430, which is a Continuation-in-part of U.S. Ser. No. 08/061,695 filed May 12,
1993 (abandoned).

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10 (BMP-10) proteins and processes for producing
them are disclosed. DNA molecules encoding the BMP-10 proteins are also disclosed. The proteins
may be used in the treatment of bone and cartilage defects and in wound healing and related
tissue repair.

L7: Entry 36 of 46

File: USPT

Dec 30, 1997

DOCUMENT-IDENTIFIER: US 5703043 A
TITLE: Bone morphogenetic protein-10 (BMP-10) compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

37. Document ID: US 5700911 A

L7: Entry 37 of 46

File: USPT

Dec 23, 1997

US-PAT-NO: 5700911
DOCUMENT-IDENTIFIER: US 5700911 A
TITLE: Bone morphogenetic protein -11 (BMP-11) compositions
DATE-ISSUED: December 23, 1997

US-CL-CURRENT: 530/350; 435/69.4, 530/399, 930/120

APPL-NO: 8/ 452772
DATE FILED: May 30, 1995

PARENT-CASE:
This application is a Divisional of U.S. Ser. No. 08/247,907 filed May 20, 1994 now U.S. Pat. No.

5,639,638, which is a continuation-in-part of U.S. Ser. No. 08/061,464 filed May 12, 1993
(abandoned).

IN: Wozney; John M., Celeste; Anthony J.

AB: Purified Bone Morphogenetic Protein-11(BMP-11) proteins and processes for producing
them are disclosed. Recombinant DNA molecules encoding the BMP-11 proteins are also disclosed.
The proteins may be useful in regulating follicle stimulating hormone, such as for
contraception. In addition, the proteins may be useful for the induction of bone, cartilage
and/or other connective tissue.

L7: Entry 37 of 46

File: USPT

Dec 23, 1997

DOCUMENT-IDENTIFIER: US 5700911 A
TITLE: Bone morphogenetic protein -11 (BMP-11) compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

38. Document ID: US 5639638 A

L7: Entry 38 of 46

File: USPT

Jun 17, 1997

US-PAT-NO: 5639638
DOCUMENT-IDENTIFIER: US 5639638 A
TITLE: DNA molecules encoding bone morpogenetic protein-11
DATE-ISSUED: June 17, 1997

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/358, 435/360, 435/364, 530/399,
536/23.4, 536/23.51, 930/120

APPL-NO: 8/ 247907
DATE FILED: May 20, 1994

PARENT-CASE:

BACKGROUND OF THE INVENTION This application is a Continuation-in-part application of Ser. No.
08/061,464 filed on May 12, 1993 presently abandoned.

IN: Wozney; John M., Celeste; Anthony J.

AB: Purified Bone Morphogenetic Protein-11 proteins and processes for producing them are
disclosed. Recombinant DNA molecules encoding the BMP-11 proteins are also disclosed. The
proteins may be useful in regulating follicle stimulating hormone, such as for contraception,
and for the induction of bone, cartilage and/or other connective tissue.

L7: Entry 38 of 46

File: USPT

Jun 17, 1997

DOCUMENT-IDENTIFIER: US 5639638 A
TITLE: DNA molecules encoding bone morpogenetic protein-11

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs. Below two in vitro assays useful in
comparison of BMP activities of novel osteoinductive molecules are described.

39. Document ID: US 5637480 A

L7: Entry 39 of 46

File: USPT

Jun 10, 1997

US-PAT-NO: 5637480
DOCUMENT-IDENTIFIER: US 5637480 A
TITLE: DNA molecules encoding bone morphogenetic protein-10
DATE-ISSUED: June 10, 1997

US-CL-CURRENT: 435/69.4; 435/252.3, 435/320.1, 435/325, 435/360, 435/364, 435/365.1, 530/399,
536/23.4, 536/23.51, 930/10

APPL-NO: 8/ 247908
DATE FILED: May 20, 1994

PARENT-CASE:
This application is a continuation-in-part application of Ser. No. 08/061,695 filed on May 12, 1993
presently abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
WO
PCT/US94/05288
May 12, 1994

IN: Celeste; Anthony J., Wozney; John M.

AB: Purified Bone Morphogenetic Protein-10 proteins and processes for producing them are
disclosed. Recombinant DNA molecules encoding the BMP-10 proteins are also disclosed. The
proteins may be used in the treatment of bone and cartilage defects and in wound healing and
related tissue repair.

L7: Entry 39 of 46
File: USPT
Jun 10, 1997

DOCUMENT-IDENTIFIER: US 5637480 A
TITLE: DNA molecules encoding bone morphogenetic protein-10

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypio property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

40. Document ID: US 5635372 A

L7: Entry 40 of 46
File: USPT
Jun 3, 1997

US-PAT-NO: 5635372
DOCUMENT-IDENTIFIER: US 5635372 A
TITLE: BMP-15 compositions
DATE-ISSUED: June 3, 1997

US-CL-CURRENT: 435/69.1; 435/252.3, 435/320.1, 435/325, 435/358, 435/360, 536/23.4, 536/23.5

APPL-NO: 8/ 446924
DATE FILED: May 18, 1995

IN: Celeste; Anthony J., Dube; Jennifer L., Lyons; Karen M., Hogan; Brigid

AB: Purified BMP-15-related proteins and processes for producing them are disclosed. DNA
molecules encoding the BMP-15-related proteins are also disclosed. The proteins may be used in
the treatment of bone and cartilage and/or other connective tissue defects and in wound healing
and related tissue repair.

L7: Entry 40 of 46
File: USPT
Jun 3, 1997

DOCUMENT-IDENTIFIER: US 5635372 A
TITLE: BMP-15 compositions

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of
these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of
Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by
researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20
cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2)
induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1)
and (2) represent characteristics associated with the osteoblast phenotype, the ability to
synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore,
to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon
treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells
correlate with the in vivo bone forming activity known for BMPs.

41. Document ID: US 5399677 A

L7: Entry 41 of 46
File: USPT
Mar 21, 1995

US-PAT-NO: 5399677
DOCUMENT-IDENTIFIER: US 5399677 A
TITLE: Mutants of bone morphogenetic proteins
DATE-ISSUED: March 21, 1995

US-CL-CURRENT: 536/23.5; 530/350, 530/399, 536/23.51

APPL-NO: 8/ 163877
DATE FILED: December 7, 1993

IN: Wolfman; Neil M., McCoy; John

AB: DNA molecules encoding mutant forms of bone morphogenetic proteins (BMP) are disclosed, The mutant forms of BMP can be produced bacterially and refolded to produce biologically active homodimers or heterodimers of BMP. A method of making such mutant BMPs is also disclosed.

L7: Entry 41 of 46

File: USPT

Mar 21, 1995

DOCUMENT-IDENTIFIER: US 5399677 A
TITLE: Mutants of bone morphogenetic proteins

DEPR:
The in vitro biological activity of the refolded bone morphogenetic proteins is monitored by the W-20 assay as set forth in Example 9. Use of the W-20-17 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with BMP [R. S. Thies et at., Journal of Bone and Mineral Research 5(2):305 (1990); and R. S. Thies et al., Endocrinology 130:1318-1324 (1992)]. W-20-17 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20-17 cells with BMP results in (1) increased alkaline phosphatase production, (2) induction of parathyroid hormone stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date the conversion of W-20-17 stromal cells to osteoblast-like cells has been observed only upon treatment with bone morphogenetic proteins. The in vivo biological activity of the refolded bone morphogenetic proteins is monitored by a modified version of the rat bone formation assay described in Sampath and Reddi, Proc. Natl. Acad. Sci. USA, 80:6591-6595 (1983) herein called the Rosenmodified Sampath-Reddi assay, as set forth in Example 10.

42. Document ID: US 5385887 A

L7: Entry 42 of 46

File: USPT

Jan 31, 1995

US-PAT-NO: 5385887
DOCUMENT-IDENTIFIER: US 5385887 A
TITLE: Formulations for delivery of osteogenic proteins
DATE-ISSUED: January 31, 1995

US-CL-CURRENT: 514/12; 106/645, 424/423, 424/426, 514/21, 514/8, 530/350, 530/397, 530/399, 530/840

APPL-NO: 8/ 119772
DATE FILED: September 10, 1993

IN: Yim; Kalvin W. K., Huberty; Michael C., Northey, Jr.; Richard P., Schrier; Jay A.

AB: A composition is disclosed comprising a pharmaceutically acceptable admixture of an osteogenic protein; a porous particulate polymer matrix; an osteogenic protein-sequestering amount of blood clot; and a calcium sulfate hemihydrate-containing substance. Also disclosed are formulations of bone morphogenetic proteins with improved solubility and/or stability characteristics.

L7: Entry 42 of 46

File: USPT

Jan 31, 1995

DOCUMENT-IDENTIFIER: US 5385887 A
TITLE: Formulations for delivery of osteogenic proteins

DEPR:
Use of the W-20 bone marrow stromal cells as an indicator cell line is based upon the conversion of these cells to osteoblast-like cells after treatment with a BMP protein [Thies et al, Journal of Bone and Mineral Research, 5:305 (1990); and Thies et al, Endocrinology, 130:1318 (1992)].
Specifically, W-20 cells are a clonal bone marrow stromal cell line derived from adult mice by researchers in the laboratory of Dr. D. Nathan, Children's Hospital, Boston, Mass. Treatment of W-20 cells with certain BMP proteins results in (1) increased alkaline phosphatase production, (2) induction of PTH stimulated cAMP, and (3) induction of osteocalcin synthesis by the cells. While (1) and (2) represent characteristics associated with the osteoblast phenotype, the ability to synthesize osteocalcin is a phenotypic property only displayed by mature osteoblasts. Furthermore, to date we have observed conversion of W-20 stromal cells to osteoblast-like cells only upon treatment with BMPs. In this manner, the in vitro activities displayed by BMP treated W-20 cells correlate with the in vivo bone forming activity known for BMPs.

43. Document ID: WO 9833515 A1

L7: Entry 43 of 46

File: EPAB

Aug 6, 1998

PUB-NO: WO009833515A1
DOCUMENT-IDENTIFIER: WO 9833515 A1
TITLE: STIMULATORY EFFECTS OF bFGF AND BMP-2 ON OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS

PUBN-DATE: August 6, 1998

INT-CL (IPC): A61K 38/18; C07K 14/50; C07K 14/51; C12N 5/06
EUR-CL (EPC): A61K038/18; C12N005/06

APPL-NO: US09802143
APPL-DATE: February 4, 1998

PRIORITY-DATA: US037111997P (February 5, 1997)

IN: DENNIS, JAMES E, CAPLAN, ARNOLD I

AB: CHG DATE=I9990617 STATUS=O>Bone marrow stroma

contains multipotential mesenchymal
progenitor cells which can differentiate into osteoblastic cells; we refer to these cells as
mesenchymal stem cells (MSCs). Basic fibroblast growth factor (bFGF) and bone morphogenetic
protein-2(BMP-2) have been implicated in the osteogenic regulatory process by virtue of their
mitogenic and differentiation activities, respectively. This study examines and compares the
effects of bFGF and BMP-2 on dexamethasone (Dex)-dependent in vitro osteogenic differentiation
of rat marrow-derived MSCS. A 6-day exposure to bFGF markedly stimulated cell growth and
induced osteoblastic differentiation as shown by osteocalcin MRNA expression (day 14), bone
nodule formation (day 18), and calcium deposition (day 18). These results indicate that bFGF
enhances both mitogenic activity and osteogenic development of Dex-treated marrow MSCS. In
contrast, BMP-2 did not induce an osteogenesis as strongly as bFGF. Thus, exposure to BMP-2
slightly increased bone nodule number and calcium content compared with the control. Exposure
of MSCs to both BMP-2 and bFGF induced expression of osteocalcin MRNA and mineralizing
bone-like nodules as early as day 11, and resulted in enhancement of bone formation more
markedly than either factor alone. Consistent with these results, porous calcium phosphate
ceramic cubes implanted in vitro, which were loaded with MSCs pre-exposed to both bFGF and
BMP-2, showed higher histologic score for bone formation than those with MSCs pre-exposed to
either bFGF or BMP-2. These data indicate that combined treatment with bFGF or BMP-2
synergistically enhances the osteogenic potency of bFGF in rat marrow MSC culture.

L7: Entry 43 of 46

File: EPAB

Aug 6, 1998

DOCUMENT-IDENTIFIER: WO 9833515 A1
TITLE: STIMULATORY EFFECTS OF bFGF AND BMP-2 ON OSTEOGENIC DIFFERENTIATION OF MESENCHYMAL STEM CELLS

44. Document ID: WO 200005344 A1, AU 9951242 A, EP 1100872 A1

L7: Entry 44 of 46

File: DWPI

Feb 3, 2000

DERWENT-ACC-NO: 2000-171427
DERWENT-WEEK: 200015

TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for treating e.g.
tumors, infertility, hematologic conditions, wounds, aging or damaged or diseased tissues

PRIORITY-DATA: 1998US-094008P (July 24, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200005344 A1	February 3, 2000	E	040	C12N005/02
AU 9951242 A	February 14, 2000		000	C12N005/02
EP 1100872 A1	May 23, 2001	E	000	C12N005/02

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 200005344A1	July 23, 1999	1999WO-US16633	
AU 9951242A	July 23, 1999	1999AU-0051242	
AU 9951242A		WO 200005344	Based on
EP 1100872A1	July 23, 1999	1999EP-0935857	
EP 1100872A1	July 23, 1999	1999WO-US16633	
EP 1100872A1		WO 200005344	Based on

INT-CL (IPC): C12N 5/02; C12N 5/06

IN: SPRADLING, A C, XIE, T

AB: NOVELTY - A method for maintaining germline stem cells of Drosophila comprises
providing a population of the germline stem cells, and stimulating signal transduction by a
bone morphogenic protein (BMP) signaling pathway in at least one cell of the population, the
stimulation maintains more germline stem cells in the population compared to a population which
has not had the signal transduction., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also
included for the following:, (1) a cell population made by the novel method, where there are at
least 10 germline stem cells in the population for each germline stem cell present prior to
stimulation of BMP signaling;, (2) a method for maintaining Drosophila stem cells comprising
providing a population comprised of the stem cells, and stimulating decapentaplegic (dpp)
signaling such that more stem cells of the population are maintained as at least viable or
undifferentiated as compared to a population of stem cells which has not been stimulated;, (3)
a method of reducing or eliminating stem cells or tumor cells of an organism comprising
regressing signal transduction by a BMP receptor pathway such that the stem cells or tumor
cells are reduced or eliminated;, (4) a method of increasing abundance of stem cells of an
organism comprising stimulating signal transduction by a BMP receptor pathway such that

abundance of at least some stem cells is increased;, (5) a method of increasing lifetime of
stem cells of an organism comprising stimulating signal transduction by a BMP receptor pathway
such that the lifetime of at least some stem cells in increased., ACTIVITY - Vulnery;
cytostatic., MECHANISM OF ACTION - Bone morphogenetic protein modulator., USE - The methods can
be used for maintaining or propagating Drosophila stem cells in vivo or in vitro. Using the
methods, it is possible to extend the life span of stem cells. Drugs that upregulate BMP
signaling to stem cells may enhance fertility in humans and animals, such as male fertility in
patients with reduced numbers of germline stem cells (basal cells). Such drugs may ameliorate
hematologic conditions caused by reduced stem cell functioning, e.g. aplastic anemias,
agammaglobulinemia, and related conditions. Drugs enhancing BMP signaling may enhance wound
healing. Aging-related pathologies caused by loss of stem cells, such as hair loss, loss of
muscle mass, reduction of blood cell numbers, and the aging of the skin and other stem
cell-dependent tissues could be treated by increasing BMP signal transduction. Compounds
enhancing BMP signaling may increase the average lifespan of an organism. Drugs inhibiting BMP
signaling pathways may be useful therapies against teratocarcinoma by causing stem cell
differentiation, e.g. drugs which inhibit BMP signaling may be successful treatments against
ovarian germline tumors dependent upon BMP signaling for continued growth. Increased or
decreased BMP signaling to stem cells might allow populations of stem cells to expand prior to
bone marrow transplant, increasing the chances of successful transplantation and reducing the
amount of donor marrow required. Further, control of BMP signaling pathways may permit stem
cells other than those in bone marrow to be removed from a patient, expanded in vitro, and
subsequently reintroduced into the patient to repair tissues damaged by injury or disease, such
as Parkinson's disease. Bone marrow from patients with hematologic tumors, such as lymphoma and
leukemia, could be tested for BMP sensitivity. Positive test results for BMP sensitivity would
allow steps to be taken to avoid potential side effects of anti-BMP treatment in vivo, e.g.
marrow removed from the patient could be cleansed of tumors cells by inhibiting BMP signaling,
thereby inducing differentiation of tumor cells and reducing the tumor burden. The cleansed
marrow would subsequently be returned to the patient in an autologous bone marrow transplant.
Such differentiation therapy could also be used for solid tumors e.g. sarcoma, carcinoma, and
neuroglioma to reduce tumor burden. Therapy may be used alone or in association with other
treatments e.g. chemotherapy, hyperthermia, or radiation, which preferentially kills rapidly
dividing cells and surgical resection of tumor. The methods can provide a model of ovarian
tumor formation in which overexpression of dpp produces ovarian stem cell tumors. In addition,
one or more genes of the stem cell may be activated or inhibited by chemical or environmental
induction, antisense, ribozyme, chimeric repair vector, RNAi, or random/sequence-specific
insertion. Ectopic expression of a gene may be controlled in a particular spatial or temporal
manner, mimic pathologic or disease states, or create phenocopies of mutations in the
endogenous gene. The methods can also be used in agriculture and wildlife conservation.

DERWENT-ACC-NO: 2000-171427
DERWENT-WEEK: 200015

TITLE: Maintaining Drosophila germline stem cells, useful for developing methods for treating e.g.
tumors, infertility, hematologic conditions, wounds, aging or damaged or diseased tissues

ABTX :
NOVELTY - A method for maintaining germline stem cells of Drosophila comprises providing a
population of the germline stem cells, and stimulating signal transduction by a bone morphogenic
protein (BMP) signaling pathway in at least one cell of the population, the stimulation maintains
more germline stem cells in the population compared to a population which has not had the signal
transduction.

ABTX:
(1) a cell population made by the novel method, where there are at least 10 germline stem cells in
the population for each germline stem cell present prior to stimulation of BMP signaling;

ABTX:
(3) a method of reducing or eliminating stem cells or tumor cells of an organism comprising
regressing signal transduction by a BMP receptor pathway such that the stem cells or tumor cells are
reduced or eliminated;

ABTX:
(4) a method of increasing abundance of stem cells of an organism comprising stimulating signal
transduction by a BMP receptor pathway such that abundance of at least some stem cells is increased;

ABTX:
(5) a method of increasing lifetime of stem cells of an organism comprising stimulating signal
transduction by a BMP receptor pathway such that the lifetime of at least some stem cells in
increased.

ABTX:
USE - The methods can be used for maintaining or propagating Drosophila stem cells in vivo or in
vitro. Using the methods, it is possible to extend the life span of stem cells. Drugs that
upregulate BMP signaling to stem cells may enhance fertility in humans and animals, such as male
fertility in patients with reduced numbers of germline stem cells (basal cells). Such drugs may
ameliorate hematologic conditions caused by reduced stem cell functioning, e.g. aplastic anemias,
agammaglobulinemia, and related conditions. Drugs enhancing BMP signaling may enhance wound healing.
Aging-related pathologies caused by loss of stem cells, such as hair loss, loss of muscle mass,
reduction of blood cell numbers, and the aging of the skin and other stem cell-dependent tissues
could be treated by increasing BMP signal transduction. Compounds enhancing BMP signaling may
increase the average lifespan of an organism. Drugs inhibiting BMP signaling pathways may be useful
therapies against teratocarcinoma by causing stem cell differentiation, e.g. drugs which inhibit BMP
signaling may be successful treatments against ovarian germline tumors dependent upon BMP signaling
for continued growth. Increased or decreased BMP signaling to stem cells

might allow populations of
stem cells to expand prior to bone marrow transplant, increasing the chances of successful
transplantation and reducing the amount of donor marrow required. Further, control of BMP signaling
pathways may permit stem cells other than those in bone marrow to be removed from a patient,
expanded in vitro, and subsequently reintroduced into the patient to repair tissues damaged by
injury or disease, such as Parkinson's disease. Bone marrow from patients with hematologic tumors,
such as lymphoma and leukemia, could be tested for BMP sensitivity. Positive test results for BMP
sensitivity would allow steps to be taken to avoid potential side effects of anti-BMP treatment in
vivo, e.g. marrow removed from the patient could be cleansed of tumors cells by inhibiting BMP
signaling, thereby inducing differentiation of tumor cells and reducing the tumor burden. The
cleansed marrow would subsequently be returned to the patient in an autologous bone marrow
transplant. Such differentiation therapy could also be used for solid tumors e.g. sarcoma,
carcinoma, and neuroglioma to reduce tumor burden. Therapy may be used alone or in association with
other treatments e.g. chemotherapy, hyperthermia, or radiation, which preferentially kills rapidly
dividing cells and surgical resection of tumor. The methods can provide a model of ovarian tumor
formation in which overexpression of dpp produces ovarian stem cell tumors. In addition, one or more
genes of the stem cell may be activated or inhibited by chemical or environmental induction,
antisense, ribozyme, chimeric repair vector, RNAi, or random/sequence-specific insertion. Ectopic
expression of a gene may be controlled in a particular spatial or temporal manner, mimic pathologic
or disease states, or create phenocopies of mutations in the endogenous gene. The methods can also
be used in agriculture and wildlife conservation.

45. Document ID: EP 1037907 A2, WO 9929718 A2, AU 9914631 A, US 6027917 A

L7: Entry 45 of 46
File: DWPI
Sep 27, 2000

DERWENT-ACC-NO: 1999-385570
DERWENT-WEEK: 200048

TITLE: New Purified bone morphogenic protein-17 and -18 (BMP-17 and BMP-18) polypeptides, useful for
the induction of growth and/or differentiation of undifferentiated embryonic and stem cells

PRIORITY-DATA: 1997US-0987904 (December 10, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1037907 A2	September 27, 2000	E	000	C07K014/00
WO 9929718 A2	June 17, 1999	E	039	C07K014/00
AU 9914631 A	June 28, 1999		000	C07K014/00
US 6027917 A	February 22, 2000		000	C12N001/21

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 1037907A2	November 17, 1998	1998EP-0958631	
EP 1037907A2	November 17, 1998	1998WO-US24613	
EP 1037907A2		WO 9929718	Based on
WO 9929718A2	November 17, 1998	1998WO-US24613	
AU 9914631A	November 17, 1998	1999AU-0014631	
AU 9914631A		WO 9929718	Based on
US 6027917A	December 10, 1997	1997US-0987904	

INT-CL (IPC): C07K 14/00; C12N 1/21; C12N 5/10; C12N 15/12; C12N 15/63

IN: CELESTE, A J, MURRAY, B L

AB: NOVELTY - Purified bone morphogenic protein (BMP) polypeptides (I), comprising amino
acids 1-224 (BMP-17) or amino acids 1-231 (BMP-18) from fully defined 366 amino acid proteins
given in the specification., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for
the following:, (1) an isolated DNA molecule (II) comprising a DNA sequence selected from:, (a)
nucleotides 1, 232, 406, 427, 751 or 796 to 1059 or 1098 of fully defined 1101 cDNA sequences
given in the specification;, (b) nucleotides encoding amino acids -142, -65, -7, 1, 109 or 124
to 211 or 224 of BMP-17;, (c) nucleotides encoding amino acids -135, -58, 1, 8, 116 or 131 to
218 or 231 of BMP-18; and, (d) naturally occurring human allelic sequences and equivalent
degenerative codon sequences of (a)-(c);, (2) a host cell transformed with (II);, (3) a vector
comprising (II) in operative association with an expression control sequence;, (4) a host cell
transformed with (3);, (5) preparation of (I);, (6) a chimeric DNA molecule comprising a DNA
sequence encoding a propeptide from a member of the TGF- beta superfamily of proteins linked in
frame to a DNA sequence encoding BMP-17 or BMP-18 comprising amino acids 1-224 of the 366
sequence given in the specification; and, (7) antibodies to BMP-17 and BMP-18., ACTIVITY -
BMP-17 and BMP-18 stimulate FSH., USE - (I) is useful for the induction of growth and/or

differentiation of undifferentiated embryonic and stem cells, and for the treatment of bone,
cartilage and other connective tissue defects including tendons, ligaments and meniscus, in
wound healing and related tissue repair, and for treatment of disorders and defects to tissues
which include epidermis, nerve, muscle, including cardiac muscle, and other tissues and wounds,
and organs such as liver, lung, epithelium, brain, spleen, cardiac, pancreas and kidney
tissue., DNA (II) is useful as probes to detect expression of (I), and the vectors are useful
for delivery of (I) to cells of a patient., NOVELTY - Purified bone morphogenic protein (BMP)
polypeptides (I), comprising amino acids 1-224 (BMP-17) or amino acids 1-231 (BMP-18) from
fully defined 366 amino acid proteins given in the specification., DETAILED DESCRIPTION -
INDEPENDENT CLAIMS are also included for the following:, (1) an isolated DNA molecule (II)
comprising a DNA sequence selected from:, (a) nucleotides 1, 232, 406, 427, 751 or 796 to 1059
or 1098 of fully defined 1101 cDNA sequences given in the specification;, (b) nucleotides
encoding amino acids -142, -65, -7, 1, 109 or 124 to 211 or 224 of BMP-17;, (c) nucleotides
encoding amino acids -135, -58, 1, 8, 116 or 131 to 218 or 231 of BMP-18; and, (d) naturally
occurring human allelic sequences and equivalent degenerative codon sequences of (a)-(c);, (2)
a host cell transformed with (II);, (3) a vector comprising (II) in operative association with
an expression control sequence;, (4) a host cell transformed with (3);, (5) preparation of
(I);, (6) a chimeric DNA molecule comprising a DNA sequence encoding a propeptide from a member
of the TGF- beta superfamily of proteins linked in frame to a DNA sequence encoding BMP-17 or
BMP-18 comprising amino acids 1-224 of the 366 sequence given in the specification; and, (7)
antibodies to BMP-17 and BMP-18., ACTIVITY - BMP-17 and BMP-18 stimulate FSH., USE - (I) is
useful for the induction of growth and/or differentiation of undifferentiated embryonic and
stem cells, and for the treatment of bone, cartilage and other connective tissue defects
including tendons, ligaments and meniscus, in wound healing and related tissue repair, and for
treatment of disorders and defects to tissues which include epidermis, nerve, muscle, including
cardiac muscle, and other tissues and wounds, and organs such as liver, lung, epithelium,
brain, spleen, cardiac, pancreas and kidney tissue., DNA (II) is useful as probes to detect
expression of (I), and the vectors are useful for delivery of (I) to cells of a patient.

L7: Entry 45 of 46

File: DWPI

Sep 27, 2000

DERWENT-ACC-NO: 1999-385570
DERWENT-WEEK: 200048
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TITLE: New Purified bone morphogenic protein-17 and -18 (BMP-17 and BMP-18) polypeptides, useful for
the induction of growth and/or differentiation of undifferentiated embryonic and stem cells

46. Document ID: WO 9835022 A1, AU 9861444 A

L7: Entry 46 of 46

File: DWPI

Aug 13, 1998

DERWENT-ACC-NO: 1998-447219
DERWENT-WEEK: 199838
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TITLE: Distinguishing between undifferentiated and differentiated mesenchymal stem cells - from
relative expression of p21CIP1, also indentifying inducers of these cells, cell competence and
agents that induce expression of bone morphogenic protein receptors

PRIORITY-DATA: 1997US-036917P (February 6, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9835022 A1	August 13, 1998	E	031	C12N005/08
AU 9861444 A	August 26, 1998		000	C12N005/08

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9835022A1	February 5, 1998	1998WO-US02137	
AU 9861444A	February 5, 1998	1998AU-0061444	
AU 9861444A		WO 9835022	Based on

INT-CL (IPC): C07K 14/495; C07K 14/51; C12N 5/08

IN: CONNOLLY, T J

AB: Undifferentiated human mesenchymal stem cells (A) are distinguished from
corresponding (partially) differentiated cells (B) by measuring upregulation of p21CIP1 (a
cyclin inhibitor protein) expression in (B). Also new are: (1) identifying an inducer (I) of
mesenchymal stem cell lineage by exposing (A) to test compound and measuring any upregulation
of p21CIP1 expression; (2) determining ability of progenitor cells to differentiate by
measuring upregulation of p21CIP1, and (3) method for identifying an agent (II) that induces
(A) to express receptors for bone morphogenic protein (BMP)., The cells are modified with a
genetic construct encoding a marker protein, especially luciferase, DNA under control of a
p21CIP1 promoter, and the level of reporter expression is correlated with p21CIP1 activity.
Alternatively, the level of constitutive expression is measured using a labelled anti-p21CIP1
antibody. (I) are growth factors, specifically BMP. Method (3) is based

on the observation that
co-expression of type I and II BMP receptors in (A) stimulates p21CIP1 transcription., USE -
The methods are used (i) for quality control to ensure that cells are really undifferentiated
and (ii) to determine competence for differentiation, particularly where intended for in vivo
tissue (bone) repair. Agents that induce high levels of p21CIP1 are potential antineoplastic
agents.

L7: Entry 46 of 46

File: DWPI

Aug 13, 1998

DERWENT-ACC-NO: 1998-447219
DERWENT-WEEK: 199838

TITLE: Distinguishing between undifferentiated and differentiated mesenchymal stem cells - from
relative expression of p21CIP1, also indentifying inducers of these cells, cell competence and
agents that induce expression of bone morphogenic protein receptors

ABTX:
Undiffer entiated human mesenchymal stem cells (A) are distinguished from corresponding (partially)
differentiated cells (B) by measuring upregulation of p21CIP1 (a cyclin inhibitor protein)
expression in (B). Also new are: (1) identifying an inducer (I) of mesenchymal stem cell lineage by
exposing (A) to test compound and measuring any upregulation of p21CIP1 expression; (2) determining
ability of progenitor cells to differentiate by measuring upregulation of p21CIP1, and (3) method
for identifying an agent (II) that induces (A) to express receptors for bone morphogenic protein
(BMP).